ARTIFICIAL NEURAL NETWORKS - A NEW APPROACH IN NON-INVASIVE MONITORING OF INFLAMMATORY BOWEL DISEASES

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ARTIFICIAL NEURAL NETWORKS - A NEW APPROACH IN NON-INVASIVE MONITORING OF INFLAMMATORY BOWEL DISEASES (Abstract): Our aim was to use artificial neural networks (ANN) for assessing inflammatory bowel disease (IBD) activity using various biological and historical data.

Material and methods: The study group included 100 patients aged 18-80 years, diagnosed with ulcerative colitis (UC) - 59% and Crohn’s Disease (CD) - 41% based on clinical, biological, imaging and histopathological criteria. Both pre-diagnosed and newly diagnosed cases were included. Study database contains multiple parameters obtained through anamnesis, physical exam, evaluation of nutritional status (body mass index), laboratory tests, imaging investigations. We built the neural network using MATLAB 7.0.

Results: The accuracy of the mathematical model was measured in terms of mean square error (MSE) and mean absolute percentage error (MAPE). Calculated MAPE values for Ulcerative Colitis Disease Activity Index (UCDAI) score and Rachmilewitz score were 52,34% and 47,15% respectively. None of the scores were estimated with excellent or high precision. The Rachmilewitz score was estimated with average accuracy because the network included currently few registered patients. All other scores were estimated with low precision.

Conclusions: The partial results obtained in the first stage of this study are encouraging given the small number of patients enrolled. Thus, for the next phases of the study, with the ongoing development of the database, we expect to achieve results with higher accuracy.

Keywords: INFLAMMATORY BOWEL DISEASE, NON-INVASIVE METHODS, ARTIFICIAL NEURAL NETWORKS.

Inflammatory bowel diseases (IBD) include Crohn's disease (CD) and ulcerative colitis (UC). IBD are chronic disorders with recurrent evolution. Complex and inaccurate methods of diagnosis and treatment are conditioned by the unknown etiopathogenesis.

Currently, the techniques used to monitor disease progression are invasive and costly. For this reason, efforts of the scientific community are focused on identifying non-invasive and cost-effective methods capable of accurately assessing disease activity.

Biomarkers are noninvasive or microinvasive, objective, fast and at a lower cost
than other techniques. An ideal biomarker for IBD should be straightforward, cheap, easy to obtain, noninvasive or micro invasive, fast and reproducible. Unfortunately, there is not yet a biomarker that satisfies all these conditions (1, 2, 3, 4, 5).

Recent studies have been published that highlight the utility of artificial neural networks and automatic learning methods in the characterization of various diseases (6, 7, 8, 9). Although the methods are promising, their application in the medical field is still on its way. Therefore, this research area is open to further exploration and can add to the originality of the published works.

The link between biological data, disease history and IBD activity is a complex biological system. Most data have multidimensional and nonlinear links with the severity of the disease. Traditional statistical calculus, such as linear regression models, are too simple to achieve reliable results due to poor statistical stability. Therefore, it is difficult to measure the severity of IBD through traditional statistical models (10). Artificial neural networks are a new computer model inspired from the functioning of human brain. They can build non-linear statistical models to deal with complex biological systems. Artificial neural networks have become a common modeling method in engineering (11). In recent years, artificial neural networks have been successfully introduced for various clinical contexts (10-12). The artificial neural network model has proved to be more accurate and with better performances than multiple logistic regression (13).

In this study, we tried to investigate the possibility of establishing a complex neural correlation between the various biological and historical data of the disease and IBD activity.

**MATERIAL AND METHODS**

The study group included 100 patients aged 18-80 years, diagnosed with UC (59%) and CD (41%) based on clinical, biological, imaging and histopathological criteria. Both pre-diagnosed and newly diagnosed cases are included in the study.

Exclusion criteria: diagnosis of colorectal cancer; ethanol consumption (≥ 50g/day for men and ≥ 30g/day for women); *Clostridium difficile* infection; neurological, renal, pulmonary, infectious or chronic heart disease.

All patients included in the study were interviewed on education, occupational status, smoker status, ethanol consumption.

**Laboratory tests.** Blood tests include the following: complete blood count with red blood cell count, erythrocyte sedimentation rate (ESR), serum fibrinogen, C reactive protein (CRP), total proteins, protein electrophoresis, sodium (Na), potassium (K), chlorine (Cl), alkaline reserve. These were taken by venous puncture and transmitted to the Hematology and Biochemistry Laboratory of "Sf. Spiridon" County Clinical Emergency Hospital in the context of patient’s routine revaluation.

Lower gastrointestinal endoscopy was performed with an Olympus EVIS EXERA II. Investigation was carried out in the context of routine reassessment of patients.

Computed tomography (CT) exam was performed and interpreted by a specialist doctor in the Radiology and Medical Imaging Department of “Sf. Spiridon” County Clinical Emergency Hospital from Iasi.

Study database contains multiple parameters obtained through: anamnesis and disease history considering environmental factors and behaviors (smoker/non-smoker, ethanol consumption, medication, alimentary behavior); physical exam and evalua-
tion of nutritional status (body mass index); laboratory tests; imaging investigations (lower gastrointestinal endoscopy, CT exam).

All personal data is confidential. The database contains patient initials, personal information and study data that can only be accessed by the research team.

Before entering the study, each patient signed an informed consent. Only patients capable of giving their consent were included. Research is not conducted on vulnerable groups.

**Artificial neural networks**

This research proposes a new approach for addressing the problem of biomarkers in inflammatory bowel diseases. Thus, an interdisciplinary method has been implemented: artificial neural networks. These systems are known in literature as "learning" systems. They can be trained with a set of well-known data (patients already evaluated) and then interrogated for new cases.

An artificial neural network can mimic a biological neural system, both structurally and functionally. The network contains an input layer, an output layer and one or more hidden layers. It is made up of a set of complex processing units (neurons) interconnected by weighted links (analogies to synapses in the nervous system). Units (neurons) receive information from other neurons. If a threshold is reached, the neuron sends information to the other connected neurons; otherwise it does not send anything. In the learning phase, data with results already known are introduced into the system and the interneuronal connection weights are updated according to a training algorithm. Training process ends when the total system error is minimal. A trained neural network extracts its calculation rules from the matrix of weights between neurons. This allows to predict the outcome of new cases that have never been introduced into the system (14, 15, 16).

In this study, we built the neural network using Matlab 7.0.

Active parameters for the input layer (i.e. those with the highest estimation power), were determined using statistical methods (t-student and chi² tests). Statistical significance was set to $p = 0.05$.

Therefore, input layer contains 25 neurons that are:

- clinical: smoker status; disease duration; number of kilograms lost in the last three months; presence of asthenia; clinical data from the scores used in the output layer (UCDAI, Rachmilewitz etc.)
- biological: white blood cells count (WBC); hemoglobin (HGB); hematocrit (HCT); platelet count (PLT); red cell distribution weight (RDW); ESR; fibrinogen; cholesterol; iron; ferritin; CRP; protein electrophoresis.

The output layer consists of the following scores: Ulcerative Colitis Disease Activity Index (UCDAI); Rachmilewitz; Ulcerative Colitis Endoscopic Index of Severity (UCEIS); Geboes (histological score); Crohn’s Disease Endoscopic Index of Severity (CDEIS); Simple Endoscopic Score for Crohn’s Disease (SES-CD).

Hidden layers were used to allow the development of complex relationships between input and output neurons. Hyperbolic tangent transfer functions were used in the hidden and output layer. Each variable was normalized in the range $(0, 1)$.

80 patients were assigned to the training cohort and 20 patients were assigned to the validation cohort.

The number of hidden layers and the number of neurons within hidden layers
were determined by a trial and error process. After repeated attempts, a four-layer network with ten neurons in each hidden layer was considered the best mathematical model.

RESULTS

A descriptive statistic for a part of the data in the input layer is shown below, describing separately the training cohort and the validation cohort (tab. I).

<table>
<thead>
<tr>
<th>TABLE I</th>
<th>Training cohort</th>
<th>Validation cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Min</td>
<td>Max</td>
</tr>
<tr>
<td>WBC</td>
<td>2,86</td>
<td>15,12</td>
</tr>
<tr>
<td>PLT</td>
<td>132</td>
<td>550</td>
</tr>
<tr>
<td>RDW</td>
<td>29</td>
<td>62</td>
</tr>
<tr>
<td>ESR 1h</td>
<td>1</td>
<td>35</td>
</tr>
<tr>
<td>CRP</td>
<td>0,1</td>
<td>31,6</td>
</tr>
</tbody>
</table>

The accuracy of the mathematical model is measured in terms of mean square error (MSE) and mean absolute percentage error (MAPE). MSE is calculated based on the desired and estimated value and then the average for all data is determined. It is used as a good fit indicator of the model. MAPE indicates the mean deviation from the desired value and is usually expressed as a percentage. The precision of a model is considered excellent if MAPE value is less than 10%.

MAPE value from 10 to 20%, from 20 to 50% and above 50% is high, medium and low accuracy (17).

The formulas of MSE and MAPE are presented below:

\[
\text{MSE} = \frac{1}{n} \sum_{i=1}^{n} (Y_i - Y_i')^2
\]

\[
\text{MAPE} = \frac{1}{n} \sum_{i=1}^{n} \left| \frac{Y_i - Y_i'}{Y_i} \right| \times 100\%
\]

where \( n \) represents the number of inputs, \( Y_i \) is the desired value for the \( i^{\text{th}} \) input, \( Y_i' \) is the calculated value for the \( i^{\text{th}} \) input.

The calculated MSE and MAPE values for the output layer scores are (tab. II):

<table>
<thead>
<tr>
<th>TABLE II</th>
<th>UCDAI</th>
<th>Rachmilewitz</th>
<th>UCEIS</th>
<th>GEBOES</th>
<th>CDEIS</th>
<th>SES-CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSE</td>
<td>0,092</td>
<td>0,065</td>
<td>0,212</td>
<td>0,342</td>
<td>0,156</td>
<td>0,301</td>
</tr>
<tr>
<td>MAPE</td>
<td>52,34%</td>
<td>47,15%</td>
<td>65,37%</td>
<td>70,23%</td>
<td>62,48%</td>
<td>69,52%</td>
</tr>
</tbody>
</table>

None of the scores were estimated with excellent or high precision. The Rachmilewitz score was estimated with average accuracy, although with a value close to the medium range upper limit.

The lack of significant results is because the network included currently few registered patients. Neural networks need hundreds, up to thousands of records to deliver significant results.

In this context, it is encouraging that Rachmilewitz score was estimated with an average accuracy. Thus, the main direction for the next phase of the study is to populate the database with as many patients as possible. This will improve accuracy of the results.

Romania is a country with limited re-
sources and restricted access to expensive medical investigations. Finding an artificial neural network system capable of non-invasively evaluating inflammatory bowel disease activity, will reduce the number and cost of invasive endoscopic and histopathological investigations.

CONCLUSIONS
The partial results obtained in the first stage of this study are encouraging, given the small number of patients enrolled. Thus, for the next phases of the study, with the ongoing development of the database, we expect to achieve results with higher accuracy.

REFERENCES


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**EVALUATION OF AGREEMENT BETWEEN FUNGAL CULTURE AND PCR FOR DIAGNOSIS OF ONYCHOMYCOSIS**

Fungal culture for diagnosis of onychomycosis has the disadvantage of being time consuming and less sensitive. PCR techniques are faster and may be more suited for diagnosing nondermatophyte mold infections. In a study by Gupta *et al*, PCR methods were compared to fungal culture to measure their agreement for detection of microorganisms causing onychomycosis. For this purpose, single samples from 167 patients with suspected onychomycosis and repeated serial samples from 43 patients were analyzed using both methods to detect 16 dermatophyte species and 5 nondermatophyte molds. Kappa statistic (κ) was used to measure the agreement between methods. Regarding the identification of all infecting organisms, the two methods showed a good agreement (κ = 0.32 for single samples and κ = 0.38 for repeated samples respectively). In the case of dermatophytes, the agreement was moderate (κ = 0.44 for single samples and κ = 0.42 for repeated samples respectively). In the case of nondermatophyte molds there was a poor agreement for single samples (κ = 0.16) but a good agreement for repeated samples (κ = 0.25). The study concluded that there was a three to four times higher risk of a false-negative result when using fungal culture compared with PCR. The authors also recommend the use of serial samples, since repeated sampling increases the agreement of nondermatophyte mold identification. (Gupta AK, Nakrieko KA. Onychomycosis Infections. Do Polymerase Chain Reaction and Culture Reports Agree? *J Am Podiatr Med Assoc* 2017; 107(4): 280-286)

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