Machine Learning Leukemia Clinical Outcome Prediction

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***Abstract*— In this study novel machine learning based neural and neuro-fuzzy prognostic models for leukemia clinical outcome prediction have been developed, based on clinical and morphometric diagnostic data. Motivation was to enable better prediction of complete cytogenetic response (CCgR) for patients with chronic myeloid leukemia, compared to traditional and well-established scoring systems. Computational intelligence and machine learning have been applied to a wide range of problems to assist in decision-making, especially artificial neural networks, fuzzy systems and powerful hybrid neuro-fuzzy approaches have already proven their strong potentials in medicine. Despite that, applications in hematology are still scarce. This prospective study included a consecutive series of patients with chronic myeloid leukemia (CML) who were started on imatinib therapy. Analysis was performed with CCgR at different time intervals as the outcome variables. Machine learning based computationally intelligent neural and neuro-fuzzy models that were developed included EUTOS score on diagnosis and one of the angiogenesis morphometric parameters. The major finding of this study is that machine learning models using the morphometric parameters, available at diagnosis of chronic phase of the CML, may improve prediction of CCgR for patients on imatinib drug therapy, in comparison particularly to the EUTOS score being the standard prognostic scoring system and regression models using the same inputs.**

***Keywords*: Chronic myeloid leukemia, Machine learning, Neural networks, Neuro-fuzzy, Imatinib mesylate, Angiogenesis, Prognosis**

I. INTRODUCTION

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disease that is characterized by genetic abnormalities arising from a reciprocal translocation t(9;22)(q34;q11) with subsequent formation of a fusion gene encoding constitutively active BCRABL tyrosine kinase, which leads to the growth of leukemia cells, an increase in the proliferation and cytokine-independent growth, inhibition of apoptosis, and linkage of alternative pathways [1][2].

Angiogenesis plays a key role in the growth of the tumor, including its potential for invasion, metastasis, and progression [3]. Obviously, angiogenesis and angiogenic factors play a significant role in the course and disease process of some leukemias, which includes chronic myeloid leukemia.

The aim of this study was to investigate abilities of machine learning in prognosis of achievement of complete cytogenetic response to tyrosine kinase inhibitor therapy in patients with chronic myeloid leukemia, while the traditional scoring systems and prognostic significance of various morphometric parameters of angiogenesis has been combined with machine learning approach. Novel machine learning based neural and neuro-fuzzy prognostic models for chronic myeloid leukemia clinical outcome prediction have been developed, based on clinical and morphometric diagnostic data.

Motivation was to enable better prediction of complete cytogenetic response (CCgR) for patients with chronic myeloid leukemia, compared to traditional and well-established scoring systems and statistical approaches. This is important since CML is largely treated with targeted drugs called tyrosine-kinase inhibitors (TKIs) which have led to dramatic improved long-term survival rates since 2001. These drugs have revolutionized treatment of the disease and allow most patients to have a good quality of life when compared to the former chemotherapy drugs. Therefore, reliable prediction regarding success of therapy for each individual CML patient gains significance.

II. MOTIVATION

Computational intelligence and machine learning have been applied to a wide range of problems to assist in decision-making. Especially artificial neural networks, fuzzy systems and powerful hybrid neuro-fuzzy approaches have already proven their strong potentials in medicine. Over the past several decades, such tools have become more and more popular for medical researchers, especially those in cancer research to predict the cancer susceptibility, recurrence and survivability [4].

This is especially important in emerging field of personalized medicine, which is often described as providing "the right patient with the right drug at the right dose at the right time" and represents tailoring of medical treatment to the individual patient characteristics, needs, and preferences [5]. Despite that, applications in hematology are still scarce. Hovewer, there are reviews of some possibilities for application of machine learning algorithms for clinical predictive modeling in stem cell transplantation [6], and onsiderations of prediction of relapse in childhood acute lymphoblastic leukemia [7]. Finally, there are published some results on clinical application of artificial intelligence in patients with chronic myeloid leukemia [8].

In this study hypothesis has been considered that machine learning based models may help to improve prediction of clinical outcome in chronic myeloid leukemia patients, in comparison to traditional widespread used statistical and scoring approaches [9]. Among the traditional prognostic scores for CML treatment outcome, the newest and best preforming EUTOS score has been considered as referential.

III. METHODOLOGY

Machine learning is an application of artificial intelligence (AI) that provides systems the ability to automatically learn and improve from experience without being explicitly programmed. Machine learning focuses on the development of computer programs that can access data and use it learn for themselves. Regarding medical applications, machine learning can be considered as a data-driven analytic approach that specializes in the integration of multiple risk factors into a predictive tool [10].

This prospective study included a consecutive series of patients with chronic myeloid leukemia (CML) who were started on imatinib therapy. Patients with CML received TKIs – imatinib in an initial dose of 400 mg/day orally. In patients with cytogenetic refractoriness or cytogenetic relapse an escalated dose of 800 mg/day of imatinib or nilotinib was applied as well as dose reductions because of toxicities according to the recommendations of the European LeukemiaNet panel.

Analysis was performed with CCgR at 6, 12, and 18 months as the outcome variables. A total of 40 patients on imatinib therapy were included in the final analysis. Of these considered patients, 25 (62.5%), 29 (72.5%), and 32 (80%), respectively, achieved CCgR at 6, 12, and 18 months after initiation of imatinib therapy.

Clinical and laboratory characteristics of the patients with chronic myeloid leukemia have been summarized in Table 1 [11]. Machine learning based computationally intelligent neural and neuro-fuzzy models that were developed included EUTOS score on diagnosis and one of the following morphometric parameters: microvascular density, length of the minor axis, area or circularity of the blood vessel.

TABLE I. CLINICAL AND LABORATORY CHARACTERISTICS OF THE GROUP OF TREATED PATIENTS WITH CHRONIC MYELOID LEUKAEMIA [11]

	N	**Median**	**Range**
Baseline characteristics of the patients			
Age	40	53.78years	29-75years
Gender (male/female)	18/22		
Palpable spleen size*(yes/no)	25/15	5.28cm	0-21cm
Baseline laboratory values			
WBC count		$135.55x10^9$/L	$20-483x10^9$/L
PLT count*(normal/increase)	24/16		
Hemoglobin*(decrease/normal)	25/15		
Peripheral blasts		1.96%	0-5.5%
Peripheral basophils		3.50%	0-7%
Peripheral eosinophils		2.60%	0-7.5%
Baseline bone marrow histology			
Megakaryocytes (not increased/increased)	22/18		
Reticulin fibrosis (absent/focal/extensive)	27/10/3		

*Reported as cm below the costal margin as assessed by palpation. *Normal platelets count: $150-450x10^9$/L. *Normal hemoglobin levels: 12-16.5g/dl.

For morphometric analysis of the microvascular structures representative bone marrow biopsies were fixed in formalin, decalcified with EDTA/HCl and embedded in paraffin wax. Hematoxylin and eosin (H&E) stained and reticulin stained slides were analyzed in order to determine number of megakaryocytes and the degree of fibrosis. Microscope samples were analyzed with Leica DMR microscope with a digital camera using the direct digitization [11].

Among the other traditional prognostic scores for CML treatment outcome, the newest European Treatment and Outcomes Study (EUTOS) score predicts complete cytogenetic remission (CCgR) after the start of therapy, which is an important predictor for the course of disease. Patients without CCgR at this point of treatment are less likely to achieve one later on and are at a high risk of progressing to blastic and accelerated phase disease.

The strongest predictors for CCgR, included in EUTOS score calculation, are spleen size and percentage of basophils. Spleen size is measured in cm under the costal margin, basophils as their percent in peripheral blood. Both need to be assessed at baseline. Their relationship to CCgR is expressed by the formula: 7 * basophils + 4 * spleen size. If EUTOS score is greater than 87, the patient is at high risk of not achieving a CCgR in the future, while a sum less than or equal to 87 indicates a low risk.

Artificial neural networks (ANNs) or connectionist systems are computing systems inspired by the biological neural networks that constitute human brains. Such systems learn (progressively improve performance on) tasks by considering examples, generally without task-specific programming.

Artificial neural network proposed as a machine learning model for prediction of CML treatment outcome is shown in Figure 2. Here, feedforward multilayer perception networks were used, which were trained in an offline batch training regime. ANN is composed of several layers: the input layer, a number of hidden layers and the output layer. Between the layers are connections containing weights. Determination of the weights is called learning or training.

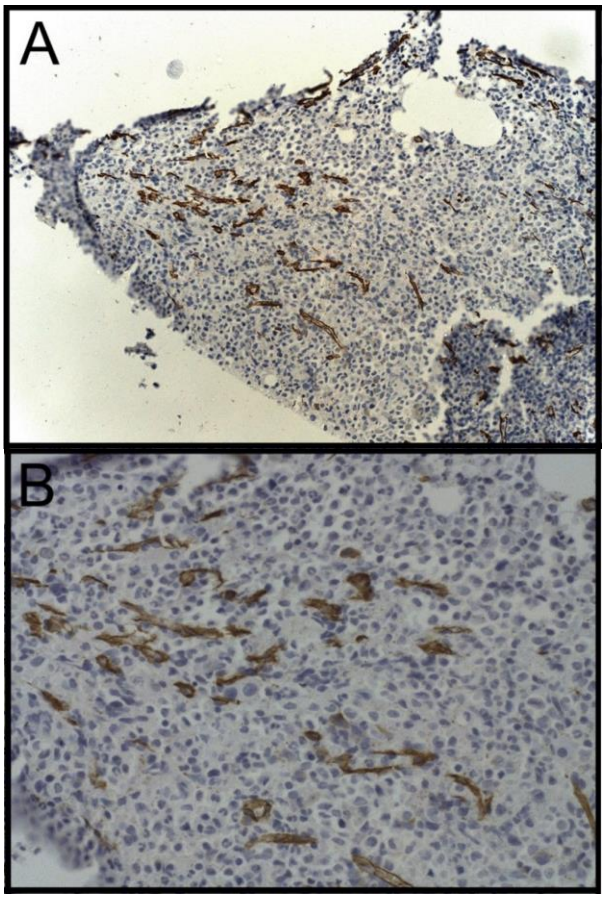

Figure 1. Immunohistochemical staining of bone marrow endothelial cells for CD34 in CML at diagnosis in case of CML patients that achieved optimal therapeutic response on therapy

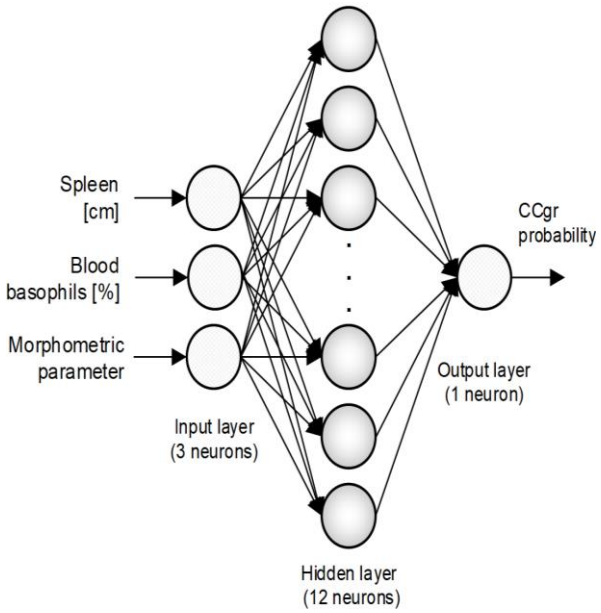

Figure 2. Feed forward neural network as machine learning prognostic model for CML treatment outcome forecast

For a multilayer perceptron, there is a computationally efficient procedure for updating the connection weights based on the technique of error backpropagation. Here, the Levenberg–Marquardt algorithm was used to train the feedforward multilayer perception network. Another important issue, generalization, shows the ability of the network to perform with newly presented data which did not form part of the training set. To achieve successful generalization, we consider three data sets: the training, test and validation sets. The ANNs used in this study had an input layer, one or two hidden layers and an output layer. Structures with up to two hidden layers were selected on the basis of vast previous experience, limited number of patients and numerous experiments and performance trials. The output of the neural network was CCgR probability. The mean squared error was used as a performance measure during training. Three inputs of the neural networks were spleen size in cm, blood basophils in percent (two variables included in EUTOS score) and one morphometric parameter selected to improve prediction [11].

Among the four selected most influential morphometric parameters mentioned before, microvascular density, length of the minor axis, area or circularity of the blood vessel, best results have been obtained with minor axis. On the other hand, inclusion of any morphometric parameter among the most influential ones tends to improve prediction, which is in line with our previous findings with other types of models [9].

Adaptive neuro-fuzzy systems represent a specific combination of artificial neural networks and fuzzy logic, thus combining the learning ability of artificial neural networks with the knowledge representation capability of fuzzy logic systems. Adaptive Neuro Fuzzy Inference System (ANFIS) consists of five layers of nodes (neurons), each of which performs a particular function on incoming signals as well as a set of parameters pertaining to this node [12]. The basic architecture of ANFIS network using hybrid learning algorithm is presented in Figure 3, which also corresponds to applied neural network prognostic models. Because of ANFIS sensitivity to larger number of inputs, here two inputs were used, EUTOS score as single variable along with single selected morphometric parameter.

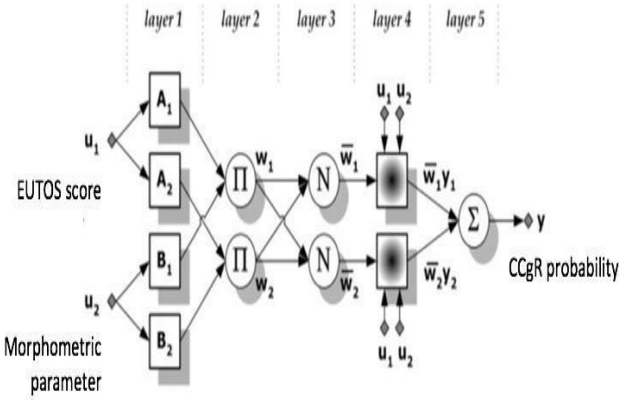

Figure 3. ANFIS network as machine learning prognostic model for CML treatment outcome forecast

ANFIS can be seen as structure equivalent to a *Radial Basis Function* (RBF) neural network. However, constructed to make use of some organizational principles resembling those of the human brain it is a hybrid structure of both fuzzy system and artificial neural network. ANFIS network has all advantages of these systems and, besides, its hybrid learning algorithm offers superior training results in comparison to other methods.

IV. DISCUSION

All analyzed patients have received imatinib mesylate as their first-line therapy for CML. Model predictions (0–1) for any individual patient were interpreted as probability of CCgR at 6, 12 or 18 months. The overall accuracy of the final model was determined by comparing the predicted values with the actual events. A probability cut-off point of 0.50 (50 %) was used to classify observations as events or non events, and patents were divided in training, validation and testing groups.

Best performing neural and ANFIS models, including EUTOS score and minor axis morphometric parameter or EUTOS containing variables spleen and basophiles and also minor axis morphometric parameter, were better than a model that includes only EUTOS score and regression model based on the same inputs. Improvement were not big but still significant, especially bearing in mind moderate number of patients that were available for study, which is common limitation with hematological diseases.

Overall model correct classification achieved for EUTOS, two input LR model, two input ANFIS model and three input ANN model were respectively 75%, 75%, 77.5% and 80%, while areas under curve on ROC graphs were 0.776, 0.829, 0.875 and 0.895 respectively. Overall models correct classifications are shown in Figure 4, together with areas under curve on ROC graphs.

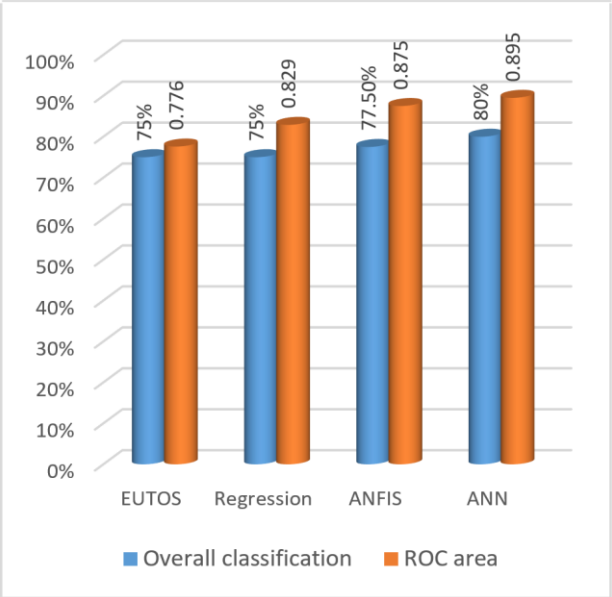

Figure 4. Comparison of performance of four different treatment outcome models for the group of 40 CML patients

The major finding of this study is that machine learning neural and ANFIS models using the morphometric parameters, available at diagnosis of chronic phase of the CML, may improve prediction of CCgR at 6, 12 and 18 months on imatinib therapy, in comparison to the EUTOS score being the standard prognostic scoring system and regression models using the same inputs.

V. CONCLUSIONS

Using machine learning based neural and neuro-fuzzy models, i.e. computationally intelligent ANN and ANFIS models with morphometric parameters in conjunction with EUTOS score or EUTOS score contained variables as inputs improves prediction of CCgR or treatment outcome in Imatinib treated CML patients.

Validation on larger groups of patients is needed, but these findings indicate that neural machine learning models could aid in individual CML patient risk stratification. This could improve CML treatment, at the same time emphasizing principles of the personalized medicine.

While the current machine learning models need to be further improved and validated before clinical use, the significant predictive value of our approach might have strong potential to provide useful information for the clinical practice, thus encouraging a computer-aided treatment perspective. This conclusion is in line with results of others cited here [6][7][8] related to hematology, as well as our recent results regarding machine learning prediction potentials in other fields of medicine [13].

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