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SIMPLE AND NON-INVASIVE LIVER FIBROSIS STAGE PREDICTION METHOD

In this paper a simple and non-expensive indirect fibrosis stage prediction method is described. Presented method is non-invasive and is based on the results of the generic blood tests. The method is based on a statistical analysis of wide range of blood tests results supported with the experience of hepatologists.

1. INTRODUCTION

Evaluation of stage of liver fibrosis in chronic type C hepatitis is very important in patient therapy. Commonly used method for fibrosis stage determination is liver biopsy, but it is an invasive method and also single biopsy does not give the confidence thus it is required to retrieve samples from more than one region of liver [1]. Some non-invasive tests methods are also available, but are expensive due to requirement of using costly, specialized blood sample markers – such commercial methods like: FibroTest by BioPredictive [2] and ELF Test by Siemens [3].

This article describes a simple and non-expensive indirect fibrosis stage prediction method, based on a generic blood test results and also the research method for biomedical data analysis for creating such methods of prediction. The predicting formula or a classifier generated using presented method should be considered as an indirect fibrosis marker.

2. MATERIAL AND MEDICAL DATA ANALYSIS METHOD

2.1. MATERIAL

The results of routine liver function tests from 63 patients with chronic hepatitis C infected with genotype 1 HCV were analysed.. Patients were qualified if they were positive for HCV antibodies and serum HCV RNA. In case of all patients, a standard liver biopsy was performed and liver specimens were evaluated according to the METAVIR classification (Fibrosis score: F0 = no fibrosis; F1 = portal fibrosis without septa; F2 = portal fibrosis with few septa; F3 = numerous septa without cirrhosis; F4 = cirrhosis) [4]. All the patients have a compensated liver disease and at the time of the study, none of the subjects was suffered from any other chronic disease. Finally, due to the incompleteness of the records only 38 records were used for regression. The clinical characteristics of these patients is presented in Table 1.

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Table 1. Clinical and biological characteristics of the 38 patients.
* mean (std. deviation).

Age* (years)	45 (15)
Male, n(%)	22 (58%)
Biopsy result, n(%)	
I	22 (58%)
II	3 (8%)
III	8 (21%)
IV	5 (13%)
PT* (sec.)	11.72 (1.07)
APTT* (sec.)	34.38 (7.28)
ALAT* (IU/L)	84.92 (62.69)
GGTP* (IU/L)	69.26 (63.23)
CRP* (IU/L)	1.08 (2.12)
Glb. α_1* (%)	2.51 (0.49)
Glb. α_2* (%)	9.21 (1.10)
Glb. β* (%)	10.30 (1.22)

2.2. PROBLEMS DURING RESEARCH

Main problem during the research was low number of data samples to analyze – it is not easy to get blood test results of patients with diagnosed chronic hepatitis C, infected with genotype1 HCV that have no other medical conditions and are not under any medical therapy. Also blood test results which were available for research were inconsistent, i.e. some patients have one set of blood tests, while other patients – have a set of other blood tests, however the sets were partially overlapping. Other important thing was the fact that the number of available blood tests (parameters) was greater than the number of patients (samples) with a complete set of tests.

2.3. PROPOSED DATA ANALYSIS METHOD

To bare with the problem of low sample count and their incompleteness, there was proposed a brute-force like algorithm to generate all possible subsets of parameters with given parameters count. This ensures the usage of all possible samples having a given set of parameters and makes possible to use multiple regression for evaluating a classifier, which requires that there is more samples than parameters in each sample ($n>k+1$).

For every n-parameter subset the regression equation (1) is evaluated and its accuracy against training set is calculated.

The equation (1) is a matrix consisting $n \times k$ elements. One row of this matrix can be formed as follows:

$$y_i^* = \alpha_0 + \alpha_1 x_{i1} + \alpha_2 x_{i2} + \ldots + \alpha_k x_{ik} \tag{1}$$

where:

y_i^*	– theoretical (predicted) value,
$\alpha_0, \ldots, \alpha_k$	– regression coefficients,
$x_{i1}, \ldots, x_{ik}$	– parameters values (independent variables),
k	– number of parameters.

In the final stage the classifier with the lowest error is chosen, but only classifiers generated using subsets having a full coverage of the possible theoretical values (fibrosis stage) and number of samples greater than number of parameters are taken into account.

The average relative error (2) has been chosen as a measure of classifier inaccuracy.

$$E_{avg\,rel} = \frac{\sum_{i=1}^{n} \left| \frac{y_i - y_i^*}{y_i} \right|}{n} \tag{2}$$

where:

y_i^* – theoretical (predicted) value,
y_i – empirical (measured) value,
n – number of samples.

3. TESTS AND RESULTS

3.1. DATA SET DESCRIPTION

Our data set contained blood test results from 64 patients who were selected by the medical staff on the basis of their medical condition – they had no other diagnosed illnesses and they were not during or just after any form of a medical therapy (they have not been taking any drugs or other medicaments). For each patient there were 41 parameters measured, including their age and sex (unfortunately not all patients had a full set of test results) and among them there were 17 parameters preselected by the doctors as a potentially important.

3.2. TESTS

Tests were performed for a full data set as well as for a preselected subset with grouping of 3 to 8 parameters. Test results for preselected data were perfectly stable – with increasing number of parameters the final classifier was always containing the same parameters with one new and also the accuracy was growing (Fig.1). The test results for full data set were less stable although for every subset size the winning classifier was repeatedly containing one parameter – CRP. As a result this parameter has been added to the set of preselected parameters and calculations were performed again, this time with slightly better accuracy and always containing the CRP parameter in the selected best classifier.

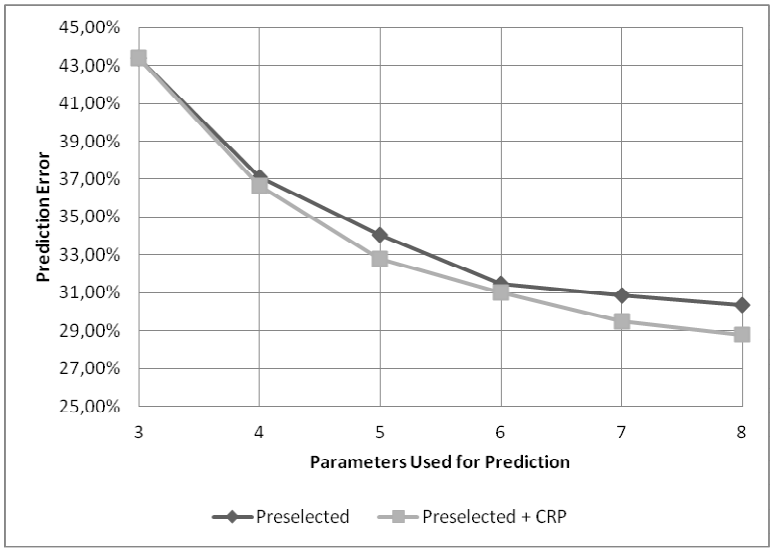

Fig. 1. Estimation error vs. number of parameters.

3.3. RESULTS

Proposed algorithm has selected the following parameters (Table 2) for the estimating the liver fibrosis stage:

Table 2. Parameters used for estimation vs. training group size.

Number of parameters		X_1	X_2	X_3	X_4	X_5	X_6	X_7	X_8	*Est. error*
6	w/ CRP	PT	APTT	GGTP	Glb. α_1	Glb. α_2	***CRP***	-	-	31.0%
	w/o CRP	PT	APTT	GGTP	Glb. α_1	Glb. α_2	***Age***	-	-	31.4%
7	w/ CRP	PT	APTT	GGTP	Glb. α_1	***Glb. α_2***	Glb. β	***CRP***	-	29.5%
	w/o CRP	PT	APTT	GGTP	Glb. α_1	***ALAT***	Glb. β	***Age***		30.9%
8	w/ CRP	PT	APTT	ALAT	GGTP	Glb. α_1	***Glb. α_2***	Glb. β	***CRP***	28.8%
	w/o CRP	PT	APTT	ALAT	GGTP	Glb. α_1	***ALP***	Glb. β	***Age***	30.4%

The selected parameters (blood tests) are:

PT – Prothrombin time,
APTT – Activated partial thromboplastin time,
ALAT – Alanine transaminase,
GGTP – Gamma glutamyl transpeptidase,
CRP – C-reactive protein,
Glb. α_1 – Alpha 1 globulins,
Glb. α_2 – Alpha 2 globulins,
Glb. β – Beta globulins.

The final result of presented algorithm is the formula (3) for calculating the liver fibrosis stage on the basis of the mentioned above blood tests results:

$$\begin{aligned} y_i^* = \; & -9{,}4538 + 0{,}5432 \cdot \mathrm{PT}_i + 0{,}0151 \cdot \mathrm{APTT}_i + 0{,}0020 \cdot \mathrm{ALAT}_i + 0{,}0029 \cdot \mathrm{GGTP}_i \\ & -0{,}0238 \cdot \mathrm{CRP}_i + 0{,}8294 \cdot \mathrm{Glb.}\alpha_{1_i} + 0{,}4156 \cdot \mathrm{Glb.}\alpha_{2_i} - 0{,}1736 \cdot \mathrm{Glb.}\beta_i \end{aligned} \tag{3}$$

On the basis of the further analysis of the result given above, performed using *STATISTICA*, the importance of the parameters has been estimated. The most important parameters were: *Prothrombin time, Gamma glutamyl transpeptidase, Alpha 1 globulins, Alpha 2 globulins*. Although these parameters were the most important ones, by introducing additional parameters to the formula, despite their lower importance, the overall estimation error was decreased.

4. CONCLUSIONS

Presented paper shows that it is possible to reach similar prediction error level to commercial tests [6]. It is also worth to mention that the error level is calculated against fibrosis stage defined on the basis of the biopsy result which is expressed as an integer value, while the formula returns a real value, so perfect match is almost impossible. It is also important liver biopsy result, according to the other research, is also only a prediction with classification error varying from 35% up to 45% [9], depending on the sample size and count.

Two interesting results may be observed from the medical point of view – one is the fact that the CRP value seems to have connection with the liver fibrosis stage and the second is the fact that the GGTP seems to be the most important parameter among Liver Function Tests in predicting liver fibrosis stage.

Our research has been done on a very low number of samples in comparison to other similar works [5-7] so it requires further validation.

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