Title: New Toll to Predict Chronic Hepatitis C Treatment Result for Each Patient

Ieva Tolmane (Corresponding author)

Latvian University, Riga, Latvia

Riga East university hospital, Infectology Center of Latvia, Riga, Latvia

Address: Linezera Street 3, Riga, Latvia, LV 1006

Phone: +371 29266740, Fax: +371 67014568

E-mail: ieva.tolmane@inbox.lv, ieva.tolmane@aslimnica.lv

Baiba Rozentale

Riga Stradin's University, Infectology and Dermatology department, Riga, Latvia

Riga East university hospital, Infectology Center of Latvia, Riga, Latvia

Address: Linezera Street 3, Riga, Latvia, LV 1006

Phone: +371 67014500, Fax: +371 67014568

E-mail: baiba.rozentale@aslimnica.lv

Jazeps Keiss

Riga East university hospital, Infectology Center of Latvia, Riga, Latvia

Address: Linezera Street 3, Riga, Latvia, LV 1006

Phone: +371 67014541, Fax: +371 67014568

E-mail: jazeps.keishs@aslimnica.lv

Andrejs Ivanovs

Riga Stradin's University, Infectology and Dermatology department, Riga, Latvia

Phone: +371 29434381

 ISSN 1661-464X

E-mail: andrejs@datuapstrade.lv

Raimonds Simanis

Riga Stradin's University, Infectology and Dermatology department, Riga, Latvia

Phone: +371 29372777

E-mail: raimonds.simanis@e-teliamtc.lv

The research is financed by European Social Found as a bursary for corresponding author.

Abstract

Background & Aims: With the standard treatment sustained virology response (SVR) can be achieved in only 54 to 63% of patients. There are many factors influencing therapy result.

The aim of this study was to develop method to prognosticate SVR in patients with chronic viral hepatitis C.

Methods: There were 264 chronic hepatitis C patients included in the study. All patients received standard treatment with interferon plus ribavirin and were divided into 2 groups – 140 (53%) responders, 124 (47%) non-responders. We analyzed 30 different factors influencing therapy result, and observed statistically significant difference in 11 factors between the groups (age, weight, BMI, GGT, insulin, IR-HOMA, fibrosis, HAI, hemosiderosis, HCV genotype and IL 28B genotype).

We used *binary logistic regression* to calculate prognosis of SVR based on standard formula: $p=1/(1+e^{-z})$, z – equation of regression, *e* – Euler's number = 2.71828.

Results: Using *binary logistic regression*, step by step the weakest independent variable was dropped out, and left 3 the most important variables – body mass index, HCV genotype and histological activity index. In this step the accuracy rate of prognosis was the highest – 78.7% (Nagelkerke R Square = 0.336).

The equation of regression:

$z = BMI \times (-0.126) + HCV\ genotype \times 2.377 + HAI\ index \times (-0.191) + 2.502$

HCV genotype 1 is coding as 1, HCV genotype 2, 3 – as 2.

Conclusions: Using binary logistic regression we can prognosticate the probability of SVR based on BMI, genotype and HAI index for every patient with the accuracy of 78.7%.

Key words: Hepatitis C, treatment, prognosis, SVR

Text

Background & Aims

Due to its distribution and clinical course, chronic viral hepatitis C (VHC) has become one of the most common infectious diseases in the world. At present the number of the infected in the world is about 170 million [1,2], but in Europe it exceeds 9 million [3]. The incidence of chronic viral hepatitis C in Latvia is relatively high. The antibody prevalence is 2.4%, HCV-RNA prevalence is 1.7% [4], which means that in Latvia there might be almost 40 000 chronic hepatitis C patients.

Hepatitis C viral infection in population has been found quite recently. The virus was discovered only in 1989 when its genome was identified. An opinion prevails that patients' getting infected started faster at the beginning of the 90ties of the past century (donors' blood was not tested) and is still going on due to the lack of vaccine. Chronic viral hepatitis C itself cannot essentially affect the patients' quality of life; however, about 20% of patients are known to develop liver cirrhosis within 10-20 years. Besides, it is impossible to say how long the patient has been infected, as well as whose disease is going to progress to develop cirrhosis and hepatocellular carcinoma (HCC) [3]. Since about 20 years have passed from the first diagnosed wave of infection, liver cirrhosis and hepatocellular carcinoma rate at present and in the nearest years is going to grow in the whole world.

When undergoing treatment, 54-63% patients can get rid of hepatitis C virus [3]. Various factors are known to affect the outcome of treatment. First of all, these are the patient's own factors and co-morbidities – age, sex, race, genetic factors, obesity, insulin resistance, diabetes mellitus, HIV infection, smoking, alcohol consumption [5,6,7,8,9,10,11,12,13,14], secondly, viral factors – genotype [3,15], viral load, thirdly, morphological changes before the therapy – fatty liver, degree of fibrosis, activity of inflammation, cirrhosis [16,17].

It is, therefore, important to find any factor influencing the treatment result and to correct it, as far as possible, prior to starting the therapy, in order to achieve maximum good therapeutic result.

The aim of the study was to determine and analyze the factors affecting chronic viral hepatitis C treatment results in order to predict the possibility of SVR.

 ISSN 1661-464X

During the study there were found the factors affecting result of chronic VHC treatment. On the basis of these factors, a treatment prognosis model for chronic viral hepatitis C was developed. The information obtained in the study can be used as the foundation for making important decisions when treating chronic VHC patients to improve the therapy result.

Methods

There were 264 chronic viral hepatitis C patients included in the study, in the period from 2009 till 2011. The diagnosis of chronic VHC was confirmed performing HCV-RNA test by PCR method. All patients were caucasians, their average age was 38 years. During study 193 (73%) patients received pegylated interferon alpha 2a 180 µg/week, 68 (25.8%) patients received pegylated interferon alpha 2b 1.5 µg/kg/week in combination with ribavirin 800 – 1200 mg/day, 2 patients received interferon alpha 2a 180 µg/week in monotherapy, 1 patient received human leucocyte interferon alpha in combination with ribavirin.

From all patients 140 (53%) were males and 124 (47%) were females. There were VHC 1st genotype detected in 185 patients (70%), 2nd or 3rd genotype was seen in 79 (30%) patients. All these group patients were divided into subgroups depending on the treatment result:

1. Responders – patients, who have responded to therapy (N=140, 53%) – have reached SVR – HCV-RNA – negative at the end of therapy and 24 weeks after completing of therapy. 75 of them were HCV 1^{st} genotype patients, 65 – 2^{nd} or 3^{rd} genotype.
2. Nonresponders – (N=124, 47%) – have not responded to therapy, have not achieved SVR. 110 of them were 1st genotype, 14 – 2^{nd} or 3^{rd} genotype patients.

In total 30 various factor's impact on the treatment result was analyzed:

1. The patient's factors (age, sex, the time from diagnosing hepatitis C until starting the therapy, co-morbidities, abdominal circumference, weight, body mass index - BMI, blood count, ALAT, GGT, cholesterol, triglycerides, TSH, glucose level, insulin, insulin resistance, ANA, formation of neutralizing antibodies against alpha interferon, interleukin 28B gene polymorphism, a patient's compliance to therapy, harmful habits – smoking, alcohol consumption).
2. Viral factors (genotype, viral load).
3. Morphological changes (fibrosis stage, activity of inflammation).

The research was confirmed by The Independent Ethics Committee for clinical investigation of drugs and pharmaceutical products in Latvia performing its functions according to GCP and applicable regulatory requirements. The work was done in accordance with the international and Latvian laws and Helsinki declaration. Before undertaking the study, each patient got acquainted with the "Information to the patient" and gave a written consent for the participation in the study by signing "Statement of consent" and "Consent for data registration".

For testing IL28B gene rs12979860 polymorphism the standard molecular-biological methods were used in blood samples: classical DNA release from blood with phenolum, for amplification of polymerase chain reaction fragments, standard sequencing with Big Dye (Applied Biosystems). Genotypes were divided into CC, CT, TC, and TT.

There was done morphological examination of the liver tissues for detection of inflammation activity and degree of fibrosis, Knodell's histological activity index (HAI) was used.

The data statistical processing was done using the computer programmes SPSS v.15.0, MedCalc v12.0 and Microsoft Office Excel v.11. For the characteristics of patients' parameters the generally accepted descriptive statistical methods were used – summary tables with columns or bar graphs; indicators of central tendency and dispersion indicators – standard deviation (SD) and standard error (SE). The meaning of parameter differences is estimated by 5% probability of statistical error, thus, if in the test results p-value was less or equal to 0.05, the differences between the studies groups were recognized as statistically significant.

For the assessment of differences several statistical tests were used – if proportional data were conformed to the normal (Gaussian) distribution, for the quantitative difference analysis between several groups there was used the *analysis of variance (ANOVA)*, between two groups – *Student's t-test*. If the data were not conformed to the normal distribution, there was extra used a nonparametric *Mann-Whitney U test* for the comparison of two samples, or *Kruskal-Wallis H test* for the comparison or three and more samples. Conformity of proportional data to the normal distribution was determined by using *Kolmogorov-Smirnov test*.

Comparing the groups according to a certain qualitative parameter, Pearson's chi-squared (χ^2) or Fisher's exact criterion 2x2 tables were used. Considering χ^2 values and the number of freedom degrees (df), p value was stated.

In calculations *odds ratio* (OR) was used. It is the ratio of probability of favourable outcome to probability of unfavourable outcome. If OR>1, then probability of favourable outcome is greater than probability of unfavourable outcome, if 0<OR<1, then probability of unfavourable outcome is greater than probability of favourable outcome. Odds ratio was calculated, using the computer program MedCalc ver. 12.0 by formula (A x D) / (B x C), where:

A – patient rate from the study group (without effect) with specific exposure;

B – patient rate from the control group (with effect) with specific exposure;

C – patient rate from the study group (without effect) without specific exposure;

D – patient rate from the control group (with effect) without specific exposure.

In case any of values A, B, C, or D were zero, odds ratio was estimated according to a modified formula which is meant for small groups of numbers – [(2A + l) x (2D + l)] / [(2B + l) x (2C + l)]. Statistical significance was determined by Fisher's criterion. 95% confidence interval (95% CI) was calculated by the formula: 95% CI = In OR ± l.96.

To determine the correlation between variables, the correlation analysis was used. The calculation method of the correlation depended on the variable scale. If variables were calculated by the linear scale, then *Pearson's correlation coefficient* was used. If one of the variables has the ordinal scale, then nonparametric *Spearman's range correlation coefficient* was used.

In the current study the following interpretation of the correlation coefficient was used:

0 = neither correlation exists;

0 – 0.2 = very low correlation;

0.2 – 0.5 = low correlation;

0.5 – 0.7 = moderate correlation;

0.7 – 0.9 = high correlation;

0.9 – 1.0 = very high correlation.

In order to find out the possible impact of independent factors on the effectiveness of therapy, *binary logistic regression* was used.

 ISSN 1661-464X

Since the dependent variable of the study *Therapy result* is binary, the *binary logistic regression* was used. The aim of binary logistic regressions is to state the probability of the event, in this case – whether a patient, due to the effect of some factors, will occur in one, or in another group, whether he/she will not respond to therapy (0), or respond (1). Probability is ranging from 0 till 1, where the border is 0.5, if probability is <0.5, then the prognosis is good for the 1st group, if ≥ 0.5, then it is good for the second group. Probability was calculated by the equation: $p=1/(1+e^{-z})$, where

$z = b_1x_1 + b_2x_2 + ... + b_nx_n + a$ (or the regression equation, x – values of independent variables, b – regression coefficients, a – regression constant).

e – mathematical constant (Euler's number) = 2.71828…

To acquire more precise results between the included independent variables there should not be any interrelations, therefore an extra correlation analysis for stating the correlation was performed.

Regression can have several methods of equation formations – *Enter*, *Forward* and *Backward*. All three were used. As the more precise was *Backward* method – it was chosen to calculate prognosis.

R^2 value is calculated by two methods – Cox & Snell and Nagelkerke R^2.

Results

To detect the factors which affect the result of therapy, all treated patients were divided depending on the outcome of therapy – responders and non-responders.

In this case from 264 patients 94 patients or 35.6% were chosen for the model from the total number of patients neither of whom had any missing variable.

In both patient groups 30 factors affecting treatment result were analyzed. Statistically significant differences ($p<0.05$) between responders and non-responders patient's groups were seen in 11 parameters (factors, independent variables) plus cirrhosis presence, see Table 1.

By applying Spearman's correlation test, it was found that there exists a close relationship between insulin resistance HOMA and insulin ($r_s=0.987$, $p<0.0001$), BMI and weight ($r_s=0.859$, $p=<0.0001$), as well as between HAI index, presence of cirrhosis and fibrosis ($r_s=0.731$, $r_s=0.463$, $p<0.0001$), thus for the regression analysis there was left one most significant or more precise variable from each pair/ group.

Table 2. depicts each model's precision by steps. The highest precision – 78.7% is in the 6th step.

In the 6th step of the model only 3 variables left the regression – the most significant HCV genotype, BMI and HAI index. The last excluded variable is IL28B genotype, whose significance is 0.139. By increasing the selection border from 0.1 till 0.14, this variable remains in the equation, but then precision of the model decreases (Table 2., 3.).

According to this model the regression equation would look like this:

$p=1/(1+e^{-z})$,

z = BMI × (-0.126) + HCV genotype × 2.377 + HAI index × (-0.191) + 2.502.

If we take patient with the following independent variables:

BMI – 24.032, HCV genotype – 2 (group 2), HAI index – 5

z = 24.032 × (-0.126) + 2 × 2.377 + 5 × (-0.191) + 2.502 = 3.272968.

Inserting in the formula, $p = 1/ (1 + e^{-3.272968}) = 1 / (1 + 0.03789) = 1 / 1.03789 = 0.9635$ or 96.35% probability that the patient will respond to therapy.

We can insert the same calculation formula in Excel file. Example, see in Table IV. In tinted table windows are placed the patient's clinical parameters (independent variables) – BMI, HCV genotype and HAI index and acquire probability of response to therapy in percentage, Table 4.

Conclusions

On the basis of 3 significant factors influencing the treatment (HCV genotype, BMI and HAI), it is possible to predict the possibility to respond to therapy for each patient by formula:

$$p = \frac{1}{1+e^{-z}}$$

z = BMI × (-0.126) + HCV genotype × 2.377 + HAI index × (-0.191) + 2.502.

Using this formula, prognosis for response to therapy can be calculated by 78.7% accuracy.

Discussion

There are many factors affecting chronic viral hepatitis C treatment results. Sometimes it is hard to prognosticate the therapy result – the probability of SVR. But as treatment is relatively expensive, relatively long lasting and not always well tolerated, patients are interested in the possible result. Until now we could say prognosis based on one particular factor, for example – HCV genotype, BMI or IL28B genotype. Based on the results of this study the predictive model of SVR is made including several treatment result affecting factors – BMI, HCV genotype and HAI index.

By putting data in Excel file it is easy to calculate probability of SVR. By the changing of independent variables for each particular patient, we can see how probability of response to therapy is changing.

For example, in HCV 3rd genotype patients with HAI 7.11 and BMI in the normal range (24), comparing it to obesity (BMI=32) – obese patient's probability of response to therapy decreases from 94.65% to 86.6%.

For patient with HCV 1st genotype and HAI index 7.11 probability of response to treatment also depends on BMI. If the patient is with normal BMI (24), the probability of his/her response to therapy is 62%, but in the obese patient (BMI=32) the probability of response to therapy considerably decreases – to 37.5%.

In patient with remarkable obesity (BMI=32) with HCV 1st genotype and considerable inflammation activity/fibrosis (HAI = 14), the probability of response to therapy is slight – only 13.86%.

On the other hand, patient with HCV 1st genotype, but normal BMI (24) and minimal inflammation activity (HAI = 2), probability for response to therapy is high – 81.35%. This result justifies to start the therapy even at slight changes in the liver not expecting when the disease progresses and the probability for treatment reduces.

Thus, prior to starting chronic hepatitis C treatment, we can state the main factors affecting therapy result – BMI, virus genotype and HAI, and prognosticate the SVR probability.

In connection with the prognosis result, it would be important to choose the individualized tactics:

1) Correction of the factors which can be affected (weight, BMI) before starting treatment of chronic hepatitis C.
2) To treat patients with slight HAI changes and normal BMI without delay in order to achieve better results.

 ISSN 1661-464X

3) To consider the usefulness of therapy for the 1st genotype patients with fibrosis/cirrhosis and obesity with pegylated interferon alpha and ribavirin. Consider adding protease inhibitor to standard treatment.

Using this model, each particular patient is able to expect the possibility of response to therapy.

References

1. Chen W, Wong T, Tomlinson G, Krahn M, Heathcote EJ. Prevalence and predictors of obesity among individuals with positive hepatitis C antibody in a tertiary referral clinic *J Hepatol* 2008;49(5):711-717.
2. Lavanchy D. The global burden of hepatitis C. *Liver Int* 2009;29:74–81
3. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatitis C virus infection. *J Hepatol* 2011;55:245–264
4. Tolmane I, Rozentale B, Keiss J, Arsa F, Brigis G, Zvaigzne A. Prevalence of viral hepatitis C in Latvia: a population based study. *Medicina* (Kaunas) 2011;47(10):532-5
5. Kau A, Vermehren J, Sarrazin C. Treatment predictors of a sustained virologic response in hepatitis B and C. *J Hepatol* 2008;49(4):634-651
6. Manns MP, McHutchison JG, Gordon SC, Rustqi VK, Shiffman M, Reindollar R et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trial. *Lancet* 2001;358:958-965
7. Muir AJ, Bornstein JD, Killenberg PG, Atlantic Coast Hepatitis Treatment Group. Peginterferon alfa-2b and ribavirin for the treatment of chronic hepatitis C in blacks and non-Hispanic whites. *N Engl J Med* 2004;350:2265
8. Bonkovsky HL, Naishadham D, Lambrecht RW, Chung RT, Hoefs JC, Nash R et al. Roles of iron and HFE mutations on severity and response to therapy during retreatment of advanced chronic hepatitis C. *Gastroenterology* 2006;131:1440–1451
9. Berg T, von Wagner M, Nasser S, Sarrazin C, Heintges T, Gerlach T et al. Extended treatment duration for hepatitis C virus type 1: comparing 48 versus 72 weeks of peginterferon-alfa-2a plus ribavirisn. *Gastroenterol* 2006;130:1086-1097
10. Dai CY, Chuang WL, Ho CK, Hsieh MY, Huang JF, Lee LP et al. Associations between hepatitis C viremia and low serum triglyceride and cholesterol levels: A community-based study. *J Hepatol* 2008;49(1):9-16
11. Khan KN, Yatsuhashi H. Effect of alcohol consumption on the progression of hepatitis C virus infection and risk of hepatocellular carcinoma in Japanese patients. *Alcohol* 2000;35:286–295

12. Mallat A, Hezode C, Lotersztajn S. Environmental factors as disease accelerators during chronic hepatitis C. *J Hepatol* 2008;48(4):657-665
13. Shiffman ML, Ghany MG, Morgan TR, Wright EC, Everson GT, Lindsay KL et al. Impact of reducing peginterferon alfa-2a and ribavirin dose during retreatment in patients with chronic hepatitis C. *Gastroenterology* 2007;132:103
14. Bendtzen K, Ainsworth M, Steenholdt C, Thomsen O, Brynskov J. Individual medicine in inflammatory bowel disease: Monitoring bioavailability, pharmacokinetics and immunogenicity of anti-tumour necrosis factor-alpha antibodies. *Scan J Gastroenterol* 2009;44: 774-781
15. Kau A, Vermehren J, Sarrazin C. Treatment predictors of a sustained virologic response in hepatitis B and C. *J Hepatol* 2008; 49:634
16. Poynard T McHutchison J, Goodman Z, Ling MH, Albrecht J. Is an 'a la carte' combination interferon alfa-2b plus ribavirin regimen possible for the first line treatment in patients with chronic hepatitis C? The ALGOVIRC Project Group. *Hepatol* 2000;31:211-218
17. Everson GT, Hoefs JC, Seeff LB, Bonkovsky HL, Naishadham D, Shiffman ML, et al. Impact of disease severity on outcome of antiviral therapy for chronic hepatitis C: lessons from the HALT-C trial. *Hepatology* 2006;44:1675–1684

Table 1. Survey of results

Nr.	Parameters	Responders n=140, 53%	Nonresponders N=124, 47%	*p*
1.	Age, <45 years, %	58.6	41.4	0.005
	Age, ≥46 years	38.9	61.1	
2.	Body weight, kg	76.78	83.54	0.005
3.	BMI, kg/m^2	25.09	27.25	0.002
4.	GGT, U/l	36.0	63.5	<0.0001
5.	Insulin, µIU/ml	8.3	11.0	0.026
6.	IR, HOMA	1.78	2.51	0.031
7.	Fibrosis stage, *Knodell*	1.0	1.56	<0.0001
8.	HAI, *Knodell*	6.38	7.11	0.038
9.	Hemosiderosis, %	1.6	9.7	0.008
10.	HCV 1st genotype, %	40.5	59.5	<0.0001
	HCV 2nd, 3rd genotype, %	82.3	17.7	
11.	IL 28B CC genotype, %	89.7	10.3	0.001
	IL 28B non-CC genotype, %	59.8	40.2	

Table 2. Classification table for *Backward* model

Observed			Predicted		
			Therapy result		Correct prognosis (%)
			Non-responders	Responders	
Step 1	Therapy result	Non-responders	13	15	46.4
		Responders	8	58	87.9
	Total (%)				75.5
Step 2	Therapy result	Non-responders	13	15	46.4
		Responders	8	58	87.9
	Total (%)				75.5
Step 3	Therapy result	Non-responders	13	15	46.4
		Responders	8	58	87.9
	Total (%)				75.5
Step 4	Therapy result	Non-responders	13	15	46.4
		Responders	6	60	90.9
	Total (%)				77.7
Step 5	Therapy result	Non-responders	13	15	46.4
		Responders	7	59	89.4
	Total (%)				76.6
Step 6	Therapy result	Non-responders	**14**	**14**	50.0
		Responders	**6**	**60**	90.9
	Total (%)				**78.7**

ISSN 1661-464X

Table 3. The variables in equation for *Backward* model

Steps		B	S.E.	Wald	Df	Sig.	Exp(B)
Step 1	Insulin resistance HOMA	-0.039	0.050	0.610	1	0.435	0.961
	BMI	-0.118	0.071	2.775	1	0.096	0.889
	HCV genotype	2.128	0.858	6.146	1	0.013	8.394
	Hemosiderin	-0.058	1.523	0.001	1	0.969	0.943
	IL28B genotype	-1.106	0.774	2.042	1	0.153	0.331
	Age group	0.004	0.643	0.000	1	**0.995**	1.004
	GGT	-0.001	0.003	0.079	1	0.779	0.999
	HAI index	-0.196	0.127	2.363	1	0.124	0.822
	Constant	4.919	4.269	1.327	1	0.249	136.832
Step 2	Insulin resistance HOMA	-0.039	0.050	0.624	1	0.429	0.961
	BMI	-0.118	0.071	2.777	1	0.096	889
	HCV genotype	2.127	0.853	6.223	1	0.013	8.389
	Hemosiderin	-0.057	1.512	0.001	1	**0.970**	0.944
	IL28B genotype	-1.106	0.774	2.044	1	0.153	0.331
	GGT	-0.001	0.003	0.079	1	0.779	0.999
	HAI index	-0.195	0.122	2.554	1	0.110	0.822
	Constant	4.920	4.264	1.332	1	0.249	137.028
Step 3	Insulin resistance HOMA	-0.039	0.050	0.622	1	0.430	0.962
	BMI	-0.118	0.071	2.785	1	0.095	0.889
	HCV genotype	2.125	0.850	6.242	1	0.012	8.370
	IL28B genotype	-1.104	0.772	2.046	1	0.153	0.331
	GGT	-0.001	0.003	0.079	1	**0.779**	0.999
	HAI index	-0.196	0.122	2.566	1	0.109	0.822
	Constant	4.802	2.909	2.725	1	0.099	121.807
Step 4	Insulin resistance HOMA	-0.039	0.050	0.596	1	**0.440**	0.962

Steps		B	S.E.	Wald	Df	Sig.	Exp(B)
	BMI	-0.122	0.069	3.067	1	0.080	0.885
	HCV genotype	2.154	0.843	6.524	1	0.011	8.620
	IL28B genotype	-1.142	0.761	2.251	1	0.133	0.319
	HAI index	-0.208	0.115	3.298	1	0.069	0.812
	Constant	4.953	2.868	2.982	1	0.084	141.576
Step 5	BMI	-0.127	0.068	3.492	1	0.062	0.880
	HCV genotype	2.056	0.808	6.480	1	0.011	7.817
	IL28B genotype	-1.113	0.752	2.188	1	**0.139**	0.329
	HAI index	-0.215	0.114	3.557	1	0.059	0.807
	Constant	5.089	2.822	3.252	1	0.071	162.259
Step 6	**BMI**	-0.126	0.067	3.569	1	**0.059**	0.882
	HCV genotype	2.377	0.793	8.994	1	**0.003**	10.774
	HAI index	-0.191	0.107	3.173	1	**0.075**	0.826
	Constant	2.502	2.094	1.428	1	0.232	12.210

ISSN 1661-464X

Table 4. Prognosis model of hepatitis C response to therapy in Excel file

	BMI	1 - 1st gt. 2 - 2nd,3rd gt. HCV genotype	HAI index
	24,032	2	5
Multiply by coefficient B	-3,028032	4,754	-0,955
z-value	3,272968		
z-value * -1	-3,272968		
e	2,718281828		
e^-z	0,037893791		
e^-z + 1	1,037893791		
Probability	**96,35%**		

ISSN 1661-464X