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PATTERNS OF LIVER INJURY AND ANXIETY DEGREE IN PEDIATRIC PATIENTS WITH CHRONIC VIRAL HEPATITIS B AND C AS PREDICTORS OF LIVER FIBROSIS PROGNOSIS

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Chronic viral hepatitis B and C in pediatric patients had already became and important social problems and their peculiarities studied by scientists nowadays. In research were examined 50 patients with chronic viral hepatitis B and C and 25 healthy patients. All enrolled patients underwent to clinical examination, laboratory testing, estimation of liver fibrosis degree, degree of anxiety, de Ratio index, R-index (to determine patterns of liver injury). As a result of scientific research, the following aspects were discovered. Liver function tests (ALT, AST, ALP) were significant higher in patients witch chronic viral hepatitis B and C compared with healthy patients (p<0,001). De Ritis ratio in patients with chronic hepatitis B and C (1,01±0,05 U) were significant higher compared with healthy patients (0,84±0,01 U) (p<0,01). Estimated level of R-index was significant higher in patients with chronic viral hepatitis B and C (2,21±0,18 U) compared with healthy patients (0,78±0,05 U) (p<0,001). Patterns of liver injury were detected: cholestatic pattern – in 52,0% of children witch chronic viral hepatitis B and C, mixed pattern – in 44,0%, hepatocellular pattern – in 4,0%. The value of anxiety according to HAMA scale in patients with chronic viral hepatitis B and C was significant higher (11,18±0,76 U) compared with healthy patients – 3,2±0,17 U (p<0,001). Clinical predictors of liver fibrosis prognosis were de Ritis ratio (beta=-9,02; p=0,049), result of HAMA scale (beta=0,89; p=0,006). This research had shown predictors of progression and prediction of liver fibrosis in children with chronic viral hepatitis B and C.

Key words: *liver fibrosis prognosis, children and adolescent, chronic viral hepatitis B and C, bilirubin, pshychoemotional and pshychosomatic disorders.*

Connection of the publication with planned research works.

The scientific work is a fragment of the scientific topic: «The course of viral and bacterial infections in children, depending on genetic, immunological, metabolic and morphological factors» (state registration number – 0120U100609).

Introduction.

Chronic viral hepatitis B (CVHB) and C (CVHC) are an important medical and social problem of hepatology at the current stage. According to official data, there are about 2 million people in Ukraine suffering from chronic viral hepatitis. This problem is also relevant among children [1]. CVHB in children who were infected at birth has an asymptomatic course and is characterized by a long immunotolerant phase and does not require routine treatment [2]. However, in patients who were infected during the first years of life, the progression of CVHC is faster [3].

According to WHO reports, about 2.2-3.0% of the world's population (130-170 million people) suffer from CVHC [4]. CVHC in children is mostly asymptomatic, in 4-6% it has a progressive course with the development of fibrosis and cirrhosis of the liver [5].

Scientists conduct researches of assessing the rate of formation of liver fibrosis induced by HBV- and HCV-viruses and features of forecasting its development, however, mainly in the adult population [6, 7].

Along with that, in patients with increasing age and progression of liver fibrosis, the manifestations of clinical symptoms of asthenic, astheno-vegetative, hemorrhagic and dyspeptic syndromes, lymphadenopathy and splenomegaly syndrome, extrahepatic manifestations, as well as psycho-emotional, somatopsychic and somatoform disorders are increasing.

At the same time, the prevalence of HCV infection in respondents with mental and psychiatric disorders varies from 8% to 31%, which is significantly higher than the average population indicators (1.8%) in the USA. It should be noted that in the literature there are studies on the impact of HCV-infection on the formation of cognitive processes in children [8].

Scientific publications confirm the fact about study the somatoform, psychotic, psychosomatic, emotional spectrum in children with CVHB and CVHC, because similar studies were conducted mainly in the adult population.

Research and identification of new clinical predictors of progression and prediction of the development of liver fibrosis in children with CVHB and CVHC is an important field of studies in pediatric hepatology.

The aim of the study.

To estimate clinical and laboratory predictors of liver fibrosis progression in pediatric patients with chronic viral hepatitis B and C taking into account patterns liver injury patterns, laboratory diagnostic indexes and anxiety degree according to HAMA scale of these patients.

Object and research methods.

In the clinical course of the research, we had examined 50 patients with confirmed diagnoses of chronic viral hepatitis B and C, aged from 6 up to 17 years (mean – 11,7±0,45 years), which had formed the study group and 25 healthy children, aged from 7 up to 17 years (mean – 10,16±0,64 years), which had formed control group, in the period from October 2020 up to March 2023. In 50% (n=25) of patients of study group were confirmed chronic viral hepatitis B, also in 50% (n=25) was confirmed chronic viral hepatitis C. All patients with chronic viral hepatitis B and C underwent to dynamic observation on the basis of the communal nonprofit enterprise «Vinnytsia Regional Clinical Children's Infectious Diseases Hospital Vinnytsia Regional Council» and the Department of Pediatric Infectious Diseases of National Pirogov Memorial Medical University, Vinnytsya. The diagnoses of chronic viral hepatitis B and C were confirmed by specific diagnostic techniques (ELISA and

Table 1 – Distribution of patients of study group according to sex and age (%)

Sex							
Age group	Sex	m		f		Total	
	№	n	%	n	%	n	%
	1	3	6%	7	14%	10	20%
	2	18	36%	22	44%	40	80%
	Total	21	42%	29	58%	50	100%

Table 2 – Laboratory tests and indexes in patients of study and control group (M±m)

Laboratory parameters	Patients of study group (n=50)	Patients of control group (n=25)
ALT, IU/l	62,22±7,25***	22,72±1,64
AST, IU/l	54,86±5,49***	18,72±1,24
De Ritis Ratio, U	1,01±0,05**	0,84±0,01
ALP, IU/l	261,5±14,75***	100,08±2,89
R-index, U	2,21±0,18***	0,78±0,05
Total bilirubin, mcmol/l	13,88±1,64	11,17±0,45

Notes: * – there is a significant difference between compared and control group with p<0,05; ** – there is a significant difference between compared and control group with p<0,01; *** – there is a significant difference between compared and control group with p<0,001.

Table 3 – Laboratory tests and indexes in patients of study in control group depending on age (M; CI 95%)

Laboratory parameter	Age group	Mean	Std. Deviation	95% Confidence interval of Mean	p-value
AST, IU/l	**1**	40,8	16,03	30,86; 50,74	P1<0,05 P2<0,001 P3<0,001
	2	58,38	42,13	45,32; 71,43	
	Control	18,72	6,22	16,28; 21,16	
ALT, IU/l	**1**	38,9	33,79	17,96; 59,84	P1<0,05 P2>0,05 P3<0,001
	2	68,05	53,53	51,46; 84,64	
	Control	22,72	8,23	19,49; 25,95	
De Ritis ratio, U	**1**	1,27	0,41	1,01; 1,52	P1<0,05 P2<0,01 P3<0,05
	2	0,95	0,33	0,85; 1,06	
	Control	0,84	0,08	0,8; 0,87	
ALP, IU/l	**1**	257	83,48	205,26; 308,74	P1>0,05 P2<0,001 P3<0,001
	2	262,68	109,82	228,64; 296,71	
	Control	100,08	14,49	94,4; 105,76	
R-index, U	**1**	1,36	0,64	0,97; 1,75	P1<0,001 P2<0,01 P3<0,001
	2	2,42	1,37	2; 2,85	
	Control	0,78	0,29	0,67; 0,89	
Total bilirubin, mcmol/l	**1**	6,73	2,12	5,42; 8,04	P1<0,001 P2<0,001 P3<0,05
	2	15,66	12,36	11,84; 19,49	
	Control	11,17	2,26	10,28; 12,05	

Notes: P1 – p-values estimated between 1st and 2nd age groups of patients of study group; P2 – p-values estimated between 1st age group and patients of control group; P3 – p-values estimated between 2nd age group and patients of control group.

PCR) by detection of specific laboratory markers. Management of patients with chronic viral hepatitis B and C was performed according to international and local regulatory documents. During examination all patients underwent of collecting of anamnesis, general clinical examination, determination of the degree of liver fibrosis by non-invasive method (Fibrotest or fibroelastometry). Liver function test (ALT, AST, ALP, total bilirubin level) were estimated for all patients. De Ritis ratio (AST/ALT ratio) and R-index ((ALT/ALT ULN)/ (ALP/ALP ULN) ratio) were estimated for all patients, which were enrolled to the study [9]. Anxiety degree was estimated according to Hamilton anxiety scale (HAMA) for all patients aged more than 6 years old. Control group was formed by almost healthy children which did not have in clinical evaluation and anamnesis any signs of liver lesions, viral hepatitis B and C, drug-induced hepatitis, toxic hepatitis, metabolic diseases, obesity and hereditary hepatobiliary lesions. Data analysis was performed using the software package "R-Studio" and "Statistica 6.0" by using the methods of descriptive statistics for parametric quantities. Data were presented as mean (M) and mean error (m) for quantitative values. The reliability of the data difference was established using a paired Student's t-test. Chi-squared test was used. The difference was considered clinically significant at p<0,05. Logistic multivariate regression analysis, correlation analysis and ROC-analysis were performed according to approved techniques. The study was performed and planned in accordance with the principles, standards and norms of local ethics regulatory documents and Principles of the Declaration of Helsinki. All patients and their parents were informed and had signed ICF to participate in the clinical study.

Research results and their discussion.

Having analyzed the peculiarities of sex and age group distribution of patients of study group, were estimated that all 50 patients were divided on 2 groups depending on age. First age group were formed by children aged from 6 to 9 years – 20% (n=10) of children, while second age group (children aged from 9 to 17 years) – 80% (n=40) of patients. It was noted that, male representatives count 42% (n=21) of patients, female – 58% (n=29) of examined children **(table 1).**

After systemic analysis of sex and age distribution of patients of study group, we had analyzed peculiarities of liver function tests, de Ritis ratio and R-index value in examined patients of study and control group **(table 2)**. It was established that ALT, AST, ALP levels were significant higher in patients of study group compared with patients of control group (p<0,001). Should be noted, that de Ritis ratio in patients of study group (1,01±0,05 U) were significant higher compared with patients of control group (0,84±0,01 U) (p<0,01). Value of R-index were significant higher in patients with chronic viral hepatitis B and C (2,21±0,18 U) compared with almost healthy patients (0,78±0,05 U) (p<0,001) **(table 2).**

Also, it was estimated parameters of laboratory tests (ALT, AST, ALP, total bilirubin) and laboratory indexes (de Ritis ratio, R-index) depending on age groups of examined patients of study group **(table 3).** Total levels of AST, ALT, ALP, R-index, total bilirubin was higher in patients of 2nd age group, instead of it – de Ritis ratio was higher in patients of 1st age group **(table 3).**

Also, analysis of liver function tests (ALT, AST, ALP, direct bilirubin) and diagnostic indexes (de Ritis ratio, R-index) were performed depending on liver fibrosis stages **(table 4)**. It should be noted, that clinically significant difference between comparison and control group of some parameters with different levels of confidence have been detected **(table 4)**.

De Ritis ratio was established in all examined patients as of study and control group. It was reported

Table 4 – Laboratory tests and indexes in patients of study and control group depending on liver fibrosis stages (M±m)

Parameter	Stage of liver fibrosis						Control group (n=25)
	F0 (n=23)	F0-1 (n=8)	F1 (n=2)	F1-2 (n=8)	F2 (n=3)	F3 (n=6)	
ALT, IU/l	33,96±3,8 **	43,38±8,5 *	97,5±42,62	63,5±9,18 ***	103,33±22,17 **	161,67±24,64 ***	22,72±1,64
AST, IU/l	35,39±0,21 ***	41,38±6,36 **	82±27,07 *	55,38±9,11 ***	99,33±42,67	115,5±18,41 ***	18,72±1,24
De Ritis Ratio, U	1,17±0,09 ***	1,01±0,05 **	0,89±0,11	0,86±0,06	0,88±0,2	0,73±0,06	0,84±0,01
ALP, IU/l	223,78±14,71 ***	251±9,02 ***	253,5±8,52 ***	223,88±16,85 ***	243,67±49,5 **	482,17±41,24 ***	100,08±2,89
R-index, U	1,58±0,18 ***	1,64±0,32 *	3,71±1,71	2,63±0,26 ***	4,11±0,49 ***	3,38±0,7 ***	0,78±0,05
Total bilirubin, mcmol/l	9,88±1,81	17,34±5,91	17,15±1,15***	17,41±5,93	15,37±2,11	18,03±3,38	11,17±0,45

Notes: * – there is a significant difference between compared and control group with p<0,05; ** – there is a significant difference between compared and control group with p<0,01; *** – there is a significant difference between compared and control group with p<0,001.

that de Ritis ratio was < 1,0 in 58,0% (n=29) and >1,0 in 42,0% (n=21) in patients of study group.

According to analysis of patterns of liver injury, taking into account value of R-index, it was established, that cholestatic pattern (R-index≤2) was detected in 52,0% (n=26) of children of study group, mixed pattern (2<R-index<5) – in 44,0% (n=22) of examined patients with chronic hepatitis B and C, hepatocellular pattern (R≥5) was detected in 4,0% (n=2) of patients.

In all examined patients of study and control group we have estimated the anxiety degree using HAMA scale. It was noted, that in patients of study group (n=50) value of anxiety scale according to HAMA scale was significant higher (11,18±0,76 U) compared with patients of control group (n=25) – 3,2±0,17 U (p<0,001).

Having performed correlation analysis, it was estimated that between liver fibrosis stage and AST level was detected direct significant correlation ratio (r=0,64; p<0,001), ALT – direct significant correlation ratio (r=0,71; p<0,001), de Ritis ratio – indirect significant correlation ratio (r=-0,48;-<0,001), ALP – direct significant correlation ratio (r=0,4; p=0,004), R-index – direct significant correlation ratio (r=0,55; p<0,001), HAMA-scale – direct significant correlation ratio (r=0,91; p<0,001) **(table 5).** All other ratios between values are presented in **table 5.**

Using methods of logistic multivariate regression analysis, was reported than clinical predictors, which could affect on liver fibrosis prognosis were de Ritis ratio (beta=-9,02; p=0,049), result of HAMA scale (beta=0,89; p=0,006). The factorial logistics model was reliable with a coefficient of determination R^2=0,75 (p<0,001) **(table 6).**

Having used techniques and methods of ROC-analysis, it was noted that for pediatric patients with liver fibrosis more than F1 stage degree, according to METAVIR scale, this mathematic model is highly significant and reliable (AUC=0,981; p<0,001) **(fig.).**

Table 5 – Correlation ratios between selected parameters of examined patients of study group

Parameter	Statistic parameter	AST	ALT	De Ritis ratio	ALP	R-index	Fibrosis stage	HAMA
AST	Correlation	1	0,93	-0,34	0,53	0,72	**0,64**	0,62
	p	NA	<.001	,015	<.001	<.001	**<.001**	<.001
ALT	Correlation	0,93	1	-0,62	0,45	0,84	**0,71**	0,67
	p	<.001	NA	<.001	,001	<.001	**<.001**	<.001
deRitis ratio	Correlation	-0,34	-0,62	1	-0,06	-0,64	**-0,48**	-0,44
	p	,015	<.001	NA	,661	<.001	**<.001**	,001
ALP	Correlation	0,53	0,45	-0,06	1	-0,01	**0,4**	0,45
	p	<.001	,001	,661	NA	,966	**,004**	,001
R-index	Correlation	0,72	0,84	-0,64	-0,01	1	**0,55**	0,45
	p	<.001	<.001	<.001	,966	NA	**<.001**	,001
Fibrosis stage	Correlation	0,64	0,71	-0,48	0,4	0,55	1	0,91
	p	<.001	<.001	<.001	,004	<.001	NA	<.001
HAMA	Correlation	0,62	0,67	-0,44	0,45	0,45	**0,91**	1
	p	<.001	<.001	,001	,001	,001	**<.001**	NA

Table 6 – Evaluation of indexes as predictors of liver fibrosis >F1 stage in pediatric patients of study group

Parameter	Coefficient B	Standard error	z	p	Odds Ratio	95% conf. interval
De Ritis Ratio	-9,02	4,57	1,97	,049	0	0 – 0,94
HAMA	0,89	0,32	2,75	,006	2,43	1,29 – 4,56
Constant	-2	2,82	0,71	,478	-	-

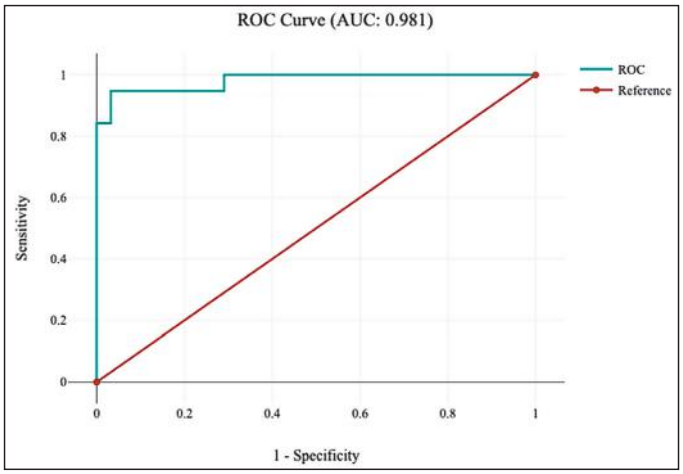

Figure – ROC-curve of analysis of mathematic prognostic model parameters depending on liver fibrosis stage.

Estimated, that cut-off point for this mathematic logistic regression model was 0,056 for patients with liver fibrosis changes more than F1 degree according to METAVIR scale. Specificity for cut-off point was 71,0%, sensitivity x 94,7% (x^2=50,09; p<0,001).

Having analyzed obtained data, we come across that we get similar results as those, which were published in scientific literature – in pediatric patients with chronic viral hepatitis B and C, as with others chronic diseases, anxiety degree rises with progression of the disease; de Ritis ratio was detected as independent predictor of liver fibrosis progression [8, 10, 11].

Conclusions.

1. Estimation of possible pattern of liver injury according to R-index will help to understand the genesis of destabilization liver parenchyma and approach in patients' management. Cholestatic pattern was detected in 52,0%, mixed pattern – in 44,0%, hepatocellular pattern – in 4,0% of patients of study group.

2. It was noted, that in patients of study group value of anxiety scale according to HAMA scale was significant higher (11,18±0,76 U) compared with patients of control group – 3,2±0,17 U (p<0,001). Also, level of anxiety increases with progression of liver fibrosis in examined patients.

3. In comparison parameters between liver fibrosis stage and AST level was detected direct correlation ratio (r=0,64; p<0,001), as between ALT (r=0,71; p<0,001), de Ritis ratio (r=-0,48;-<0,001), ALP (r=0,4; p=0,004), R-index (r=0,55; p<0,001), HAMA-scale (r=0,91; p<0,001).

4. Clinical predictors, which could affect on liver fibrosis prognosis were de Ritis ratio (beta=-9,02; p=0,049), result of HAMA scale (beta=0,89; p=0,006).

5. The cut-off point for mathematic logistic regression model was 0,056 for patients with liver fibrosis changes more than F1 degree according to METAVIR scale (specificity – 71,0%, sensitivity – 94,7% (x^2=50,09; p<0,001)).

Prospects for further research.

In further investigation, it will be necessary to examine more cohort of patients with chronic viral hepatitis B and C with estimation of additional predictors of liver fibrosis progression.

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ПАТТЕРНИ УРАЖЕННЯ ПЕЧІНКИ ТА СТУПІНЬ ТРИВОГИ У ДІТЕЙ ІЗ ХРОНІЧНИМИ ВІРУСНИМИ ГЕПАТИТАМИ В І С, ЯК ПРЕДИКТОРИ ПРОГНОЗУВАННЯ ФІБРОЗУ ПЕЧІНКИ

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Резюме. Хронічні вірусні гепатити В і С є важливою медико-соціальною проблемою гепатології на сучасному етапі. Дослідження нових клінічних предикторів прогресування і прогнозування виникнення фіброзу печінки у дітей із хронічними вірусними гепатитами В і С є актуальним полем для досліджень у дитячій гепа-

тології. Мета дослідження: визначити клінічні та лабораторні предиктори прогресування фіброзу печінки у пацієнтів дитячого віку із хронічними вірусними гепатитами В і С, беручи до уваги паттерни ураження печінки, лабораторні діагностичні індекси та ступінь тривоги за шкалою HAMA цих пацієнтів. У ході клінічного дослідження було обстежено 50 пацієнтів із підтвердженими діагнозами хронічних вірусних гепатитів В та С (середній вік – 11,7±0,45 років), які сформували досліджувану групу, та 25 практично здорових дітей (середній вік – 10,16±0,64 років), які сформували групу контролю. Рівні АЛТ, АСТ, ЛФ були достовірно вищими у пацієнтів досліджуваної групи при порівнянні із групою контролю (p<0,001). Варто зазначити, що величина індексу де Рітіса у пацієнтів досліджуваної групи (1,01±0,05 Од.) була достовірно вищою при порівнянні із пацієнтами групи контролю (0,84±0,01 Од.) (p<0,01). Величина R-індексу була достовірно вищою у пацієнтів із хронічними вірусними гепатитами В і С (2,21±0,18 Од.) порівняно із практично здоровими дітьми (0,78±0,05 Од.) (p<0,001). Щодо аналізу паттернів ураження печінки, беручи до уваги величину R-індексу, встановлено, що холестатичний паттерн визначався у 52,0% дітей досліджуваної групи, змішаний паттерн – у 44,0%, гепатоцелюлярний паттерн – у 4,0% пацієнтів. Варто зазначити, що у пацієнтів досліджуваної групи (n=50) ступінь тривоги за шкалою HAMA був достовірно вищим (11,18±0,76 Од.) порівняно із групою контролю (n=25) – 3,2±0,17 Од. (p<0,001). Клінічні предиктори, які можуть впливати на прогноз фіброзу печінки є: індекс де Рітіса (beta=-9,02; p=0,049), результати тесту за шкалою HAMA (beta=0,89; p=0,006). Точка відсічення для математичної моделі логістичної регресії становила 0,056 для пацієнтів із ступенем фіброзних змін печінки більше ніж F1 за шкалою METAVIR (специфічність – 71,0%, чутливість – 94,7% (x^2=50,09; p<0,001)).

Ключові слова: прогнозування фіброзу печінки, діти та підлітки, хронічні вірусні гепатити В і С, білірубін, психоемоційні та психосоматичні розлади.

PATTERNS OF LIVER INJURY AND ANXIETY DEGREE IN PEDIATRIC PATIENTS WITH CHRONIC VIRAL HEPATITIS B AND C AS PREDICTORS OF LIVER FIBROSIS PROGNOSIS

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Abstract. Chronic viral hepatitis B and C are an important medical and social problem of hepatology at the current stage. Research and identification of new clinical predictors of progression and prediction of the development of liver fibrosis in children with chronic viral hepatitis B and C is an important field of studies in pediatric hepatology. The aim of the study: to estimate clinical and laboratory predictors of liver fibrosis progression in pediatric patients with chronic viral hepatitis B and C taking into account patterns liver injury patterns, laboratory diagnostic indexes and anxiety degree according to HAMA scale of these patients. In the clinical course of the research, we had examined 50 patients with confirmed diagnoses of chronic viral hepatitis B and C (mean – 11,7±0,45 years), which formed study group, and 25 healthy children (mean – 10,16±0,64 years), which formed control group. ALT, AST, ALP levels were significant higher in patients of study group compared with patients of control group (p<0,001). Should be noted, that de Ritis ratio in patients of study group (1,01±0,05 U) were significant higher compared with patients of control group (0,84±0,01 U) (p<0,01). Value of R-index were significant higher in patients with chronic viral hepatitis B and C (2,21±0,18 U) compared with almost healthy patients (0,78±0,05 U) (p<0,001). According to analysis of patterns of liver injury, taking into account value of R-index, cholestatic pattern was detected in 52,0% of children of study group, mixed pattern – in 44,0%, hepatocellular pattern was detected in 4,0% of patients. It was noted, that in patients of study group (n=50) value of anxiety scale according to HAMA scale was significant higher (11,18±0,76 U) compared with patients of control group (n=25) – 3,2±0,17 U (p<0,001). Clinical predictors, which could affect on liver fibrosis prognosis were de Ritis ratio (beta=-9,02; p=0,049), result of HAMA scale (beta=0,89; p=0,006). The cut-off point for mathematic logistic regression model was 0,056 for patients with liver fibrosis changes more than F1 degree according to METAVIR scale (specificity – 71,0%, sensitivity – 94,7% (x^2=50,09; p<0,001)).

Key words: liver fibrosis prognosis, children and adolescent, chronic viral hepatitis B and C, bilirubin, pshychoemotional and pshychosomatic disorders

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