UDC 616.36-03.826-002.2-053-07-037
DOI https://doi.org/10.32689/2663-0672-2023-2-2

Iryna NEZGODA
D.S., Professor, Head of the Department of Pediatric Infectious Diseases, National Pirogov Memorial Medical University, Vinnytsya, Pyrohova 56 Street, Vinnitsya, Ukraine, 21000
ORCID: *https://orcid.org/0000-0002-7925-3398*

Yaroslav DEMCHYSHYN
Assistant Department of Pediatric Infectious Diseases, National Pirogov Memorial Medical University, Vinnytsya, Pyrohova 56 Street, Vinnitsya, Ukraine, 21000
ORCID: *https://orcid.org/0000-0002-9816-8260*

Ірина НЕЗГОДА
доктор медичних наук, професор, завідувачка кафедри дитячих інфекційних хвороб, Вінницький національний медичний університет імені М. І. Пирогова, вул. Пирогова 56, Вінниця, Україна, 21000

Ярослав ДЕМЧИШИН
асистент кафедри дитячих інфекційних хвороб, Вінницький національний медичний університет ім. М. І. Пирогова, вул. Пирогова 56, м. Вінниця, Україна, 21000

Bibliographic description of the article: Nezgoda, I., Demchyshyn, Y. (2023). Suchasni markery fibrozu pechinky u ditei, khvorykh na khronichni virusni hepatyty B i S [Modern diagnostic markers of liver fibrosis in children with chronic viral hepatitis B and C]. *Suchasna medytsyna, farmatsiia ta psykholohichne zdorovia – Modern medicine, pharmacy and psychological health*, *2 (11)*, 12–17. DOI: https://doi.org/10.32689/2663-0672-2023-2-2

Бібліографічний опис статті: Незгода І., Демчишин Я. Modern diagnostic markers of liver fibrosis in children with chronic viral hepatitis B and C. *Сучасна медицина, фармація та психологічне здоров'я.* 2023. Вип. 2 (11). С. 12–17. DOI: https://doi.org/10.32689/2663-0672-2023-2-2

MODERN DIAGNOSTIC MARKERS OF LIVER FIBROSIS IN CHILDREN WITH CHRONIC VIRAL HEPATITIS B AND C

Abstract. *The article contains scientific data about modern markers of liver fibrosis in children with chronic viral hepatitis B and C such as: FABP-1-L, arginase-1 and YKL-40.*

The aim of study: to evaluate the level of arginase-1 in children with chronic viral hepatitis B and C.

Material and methods: 40 patients with diagnoses of chronic viral hepatitis B and C (mean age – 11,48±0,6 years) were examined. All patients underwent of collecting of anamnesis, clinical examination, determination of the degree of liver fibrosis. Level of arginase-1 was performed by ELISA. Data analysis was performed using the software package "Statistica 8.0". The reliability of the data difference was established by paired Student's t-test. The difference was considered significant at p<0,05.

Results: In examined patients of study group level of Arg-1 was significant higher (108,58±4,9 ng/ml) compared with patients of control group (76,48±6,09 ng/ml) (p<0,001). Arg-1 level in male representatives was higher in both groups. Level of Arg-1 among patients of study and control group increased with increasing of patients' age. The level of Arg-1 in children of study group with oncological diseases was higher (115,24±6,2 ng/ml), compared with children without this factor (96,22±7,14 ng/ml). Level of Arg-1 was significant higher in patients with liver fibrosis F0 (124,07±7,7 ng/ml; p<0,001), F1 (106,55±0,15 ng/ml; p<0,001), F1-2 (106,07±8,5 ng/ml; p<0,01), F2 (89,44 ng/ml; p<0,05) compared with control group (76,48±6,09 ng/ml). Correlation between Arg-1 level and liver fibrosis degree was detected among patients of study group (R=-0,49; p=0,001).

Conclusion: Arginase-1 – important marker that should be studied by scientists nowadays to understand the pathogenesis of fibrogenesis of the liver.

Key words: *markers of fibrogenesis (FABP-1, Arginase-1, YKL-40), children and adolescents, chronic viral hepatitis B and C, liver fibrosis, jaundice.*

СУЧАСНІ МАРКЕРИ ФІБРОЗУ ПЕЧІНКИ У ДІТЕЙ, ХВОРИХ НА ХРОНІЧНІ ВІРУСНІ ГЕПАТИТИ В І С

Анотація. *У статті наведено наукові дані про сучасні маркери фіброзу печінки у дітей з хронічними вірусними гепатитами В і С, такі як: FABP-1-L, аргіназа-1 та YKL-40.*

Мета дослідження: оцінити рівень аргінази-1 у дітей з хронічними вірусними гепатитами В і С.

Матеріал і методи: обстежено 40 пацієнтів з діагнозом хронічних вірусних гепатитів В і С (середній вік – 11,48±0,6 років). Усім хворим проводили збір анамнезу, клінічне обстеження, визначення ступеня фіброзу печінки. Рівень аргінази-1 визначали методом ELISA. Аналіз даних проводили за допомогою програмного забезпечення «Statistica 8.0». Достовірність різниці даних встановлювали за допомогою парного t-критерію Стьюдента. Різницю вважали достовірною при p<0,05.

Результати: у обстежених пацієнтів основної групи рівень Arg-1 був достовірно вищим (108,58±4,9 нг/мл) порівняно з пацієнтами контрольної групи (76,48±6,09 нг/мл) (p<0,001). Рівень Arg-1 у представників чоловічої статі був вищим в

обох групах. Рівень Arg-1 у пацієнтів досліджуваної та контрольної груп зростав зі збільшенням віку пацієнтів. Рівень Arg-1 у дітей основної групи з онкологічними захворюваннями був вищим (115,24±6,2 нг/мл), порівняно з дітьми без даного фактора (96,22±7,14 нг/мл). Рівень Arg-1 достовірно вищий у хворих на фіброз печінки F0 (124,07±7,7 нг/мл; p<0,001), F1 (106,55±0,15 нг/мл; p<0,001), F1-2 (106,07±8,5 нг/мл; p<0,01), F2 (89,44 нг/мл; p<0,05) порівняно з контрольною групою (76,48±6,09 нг/мл). У хворих основної групи встановлено кореляційний зв'язок між рівнем Arg-1 та ступенем фіброзу печінки (R=-0,49; p=0,001).

Висновок: Аргіназа-1 – важливий маркер, який підлягає вивченню сьогодні для розуміння патогенезу фіброзу печінки.

Ключові слова: *маркери фіброгенезу (FABP-1, аргіназа-1, YKL-40), діти та підлітки, хронічні вірусні гепатити В і С, фіброз печінки, жовтяниця.*

Introduction. Chronic viral hepatitis B (CVHB) and C (CVHC) had already became an important medical problem in the field of pediatrics in modern world. About 4,000 cases of viral hepatitis B among children are registered in Ukraine every year. In children, the frequency of chronic hepatitis clearly correlates with the age of getting infected, and is maximum (up to 90%) in the first year of life and in early childhood. It was reported that CVHB and CVHC among childhood respondents have an anicteric clinical course.

CVHB in children, who were infected at birth, has an asymptomatic course and is characterized by a long immunotolerant phase and does not require medical interventions for its management [1]. At the same time, in patients who were infected during the first years of life, the progression of CVHB is faster [2].

According to official WHO reports, about 2,2–3,0% of the world's population suffers from CVHC [3]. CVHC in children is mostly asymptomatic, in 4–6% it has a progressive course with the development of fibrous changes and liver cirrhosis [4].

The rate of formation of the progressive course of CVHB and CVHC in children is determined by the pathophysiological features and dynamics of liver fibrogenesis. The rates of progression of liver fibrosis are individual and are determined by both host factors (genetic, immunological, metabolic, etc.) and by virus factors (virus genotype, viral load, etc.) [5].

Researches for new markers of non-invasive laboratory diagnosis of liver fibrosis in children, it is relevant for various pathological conditions, including CVHC and CVHB (for example, determining the level of fatty acid-binding protein (FABP-1-L), cartilage glycoprotein (YKL-40, gp39), arginase-1 and others), were performed.

YKL-40 (human cartilage glycoprotein-39, human gp-39) is a described glycoprotein that belongs to the chitinase family. It was noted that the deterministic function of YKL-40 is tissue remodeling and extracellular matrix degradation. Along with that, this biomarker is a fibroblast growth factor and acts synergistically with insulin-like growth factor-1 (IGF-1) in stimulating growth and determination, acts as an inducer of endothelial cell chemotaxis, modulates the morphological aspect of vascular endothelium, which confirms the role of this protein in neoangiogenesis, and is also associated with the macrophage inflammatory process, affects the progression of atherosclerosis, liver damaging [6; 7; 8].

At the current stage, the biological function of YKL-40 is not known for certain and is being studied by scientists in various pathological conditions, including liver diseases, breast cancer, and colorectal cancer [9; 10; 11].

According to the researches of Yamamoto N. et al., Del Turco S. et al., it was established that serum levels of YKL-40 are associated with long-term processes of fibrogenesis, and in a complex with galectin-3 can be correlated with the progression of liver fibrosis [12; 13].

According to Yoowon Kwon et al., the levels of YKL-40 in 479 examined children were determined and their relationships with the blood lipid spectrum were substantiated. It was established that the median YKL-40 of the examined cohort of patients is – 21,350 pg/mL [IQR 17,4–27,410 pg/mL], and by comparing this value between groups of patients with normal body weight, overweight and obesity, multivariate regression analysis established relationships: with the level of triglycerides (b=0.246; p=0.001), the ratio of triglycerides to HDL (b=0.03; p=0.002), the logarithmic ratio of triglycerides to HDL (b=0.209; p=0.001) [14]. In the scientific studies, there are isolated data on the study of this biomarker of liver fibrosis in children.

In addition, fatty acid binding protein (FABP) is a marker of liver fibrosis. It is a member of the lipid chaperone fatty acid binding protein family. Although all lipid-binding peptides are involved in the induction of inflammation in the metabolic syndrome, FABP levels have been shown to be associated with liver damage [15]. The results of scientific studies by Li HL et al., Pillai SS et al., also demonstrated the pathological role of FABP in the clinical course of liver fibrosis, and determined FABP as a sensitive clinical predictor of acute or chronic liver failure caused by alcohol [16; 17]. According to Rakela JL et al., FABP-1 levels were elevated in patients with acute liver injury, and FABP-1 levels above 350 ng/mL were associated with a clinically significant risk of death. FABP-1 may be a useful prognostic biomarker that can improve the current MELD, KCC diagnostic scales [18].

According to Watt J. et al., it was found that patients with liver steatosis have clinically significant lower levels of FABP-1 compared to healthy respondents [19]. According to Eguchi A. et al., the AUC value of 0.744

(95% CI: 0.6759–0.8116; p<0.0001) for serum FABP-IL was determined by ROC analysis. It was found that the cut-off level of FABP-I was 7.7 ng/ml. Patients with a level above 7.7 ng/ml had lower survival rates compared to patients with a level < 7.7 ng/ml (p<0.0001) [20].

Arginase-1 (Arg1) is another important marker that is being studied by scientists today to clarify the pathogenesis of fibrogenesis. Macrophage-specific expression of arginase-1 is thought to promote inflammation, fibrosis, and wound healing by enhancing production of L-proline, polyamine and Th2-activating cytokines [21]. Arg1 is a cytosolic enzyme that is constitutively expressed in the liver, where it is involved in nitrogen elimination by catalyzing the hydrolysis of arginine to urea and ornithine. Urea production removes excess nitrogen from the body, while L-ornithine can be used to generate polyamines, glutamate and proline, the latter of which is critical for collagen synthesis [21].

Based on the results of Kitowska K. et al., it was established that the depletion of L-arginine level due to increased expression of arginase-1 can affect cell functions in several ways. First, a sharp decrease in free L-arginine leads to a decrease in its bioavailability for NOS, thus leading to a decrease in the biosynthesis of NO. It has also been demonstrated that reduced levels of NO lead to the proliferation of smooth muscle cells and vessels, which are characteristic of fibrogenesis processes. Secondly, enhanced formation of L-ornithine by arginases increases the bioavailability of polyamines and L-proline, necessary regulators of cell proliferation and collagen synthesis [22].

According to the results of A. Chrzanowska et al., during the examination of 60 adult patients with liver cirrhosis, it was established that the level of Arg1 varied from 41,8 to 888,5 U/g, the average level of Arg1 was 1305,8±515,2 U/g. Enzyme activity in patients with cirrhosis of the liver class A (according to the Child-Pugh classification) was at the level of 791,0±130,3 U/g, in patients with class B – 473,1±148,3, and with class C 121,1±57,2 U/g [23].

It was reported that the results of research on the level of arginase-1 among pediatric patients with chronic viral hepatitis B and C were not presented in general.

The aim of study. to evaluate the level of arginase-1 in children with chronic viral hepatitis B and C depending on nosological form, sex, age, concomitant oncological disease in anamnesis and degree of liver fibrosis.

Material and methods. In the clinical course of the research, we had examined 40 patients with confirmed diagnoses of chronic viral hepatitis B and C, aged from 5 up to 17 years (mean – 11,48±0,6 years), which had formed the study group and 20 healthy children, aged from 5 up to 17 years (mean – 8,9±0,69 years), which had formed control group, in the period from October 2020 up to May 2023. In 50% (n=20) of patients of study group were confirmed chronic viral hepatitis B, also in 50% (n=20) was confirmed chronic viral hepatitis C. All patients with chronic viral hepatitis B and C underwent to dynamic observation on the clinical basement 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 clinical diagnoses of chronic viral hepatitis B and C were confirmed by specific diagnostic techniques (ELISA and PCR). Management of enrolled patients with chronic viral hepatitis B and C was performed according to 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). Total level of arginase-1 was performed by ELISA (Human ARG1 (Arginase-1) ELISA Kit (FineTest, China)). Technique of Arginase-1 detection by ELISA was performed by manufacturer (FineTest, China). For all blood samples which were tested by Human ARG1 (Arginase-1) ELISA Kit standard calibrated curve was formed (ng/ml). Control group was formed by almost healthy children which did not have in clinical evaluation and anamnesis any signs of liver damaging, 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 "Statistica 8.0" by using the methods of descriptive statistics for parametric quantities. Data were presented as mean (M) and mean error (m) for quantitative values. Correlation assay were performed. The reliability of the data difference was established using a paired Student's t-test. The difference was considered clinically significant at p<0,05. 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.

Results and their discussion. In the process of scientific research, 40 patients with CVHB and CVHC (group I) and 20 almost healthy children (group II) were examined. It is was noted that among the patients of the I group 50,0% (n=20) were patients with diagnosis of CVHB, and 50,0% (n=20) with CVHC (Table 1). The mean of age of examined patients with CVHB was 11,05±0,78 years, and children with CVHC – 11,9±0,92 years. Among the examinees of the study group, boys predominated – 65,0% (n=26), and girls – 35,0% (n=14). Along with that, an analysis of the distribution of the examined patients of the study group

by age groups was carried out: 3 children belonged to the first age group (up to 6 years), 7 patients belonged to the second (from 6 to 9 years), and to the third group (from 9 to 17 years) – 30 examined patients (Table 1).

Among enrolled patients of study group, was determined that the degree of liver fibrosis F0 according to Metavir diagnostic scale was diagnosed in 40,0% (n=16) of patients, F0-1 – in 17,5% (n=7) of children, F1 – in 5,0% (n= 2) of examined, F1-2 – in 22,5% (n=9), F2 – in 2,5% (n=1) and F3 – in 12,5% (n=5) of respondents.

In all examined patients of study and control group we have estimated the level of arginase-1 (Arg1; Human ARG1 (Arginase-1) ELISA Kit (FineTest, China)). It was noted, that in patients of study group (n=40) level of Arg-1 was significant higher (108,58±4,9 ng/ml) compared with patients of control group (n=20) – 76,48±6,09 ng/ml (p<0,001).

It was reported that in patients with CVHB (n=20) the level of Arg1 was – 105,87±8,3 ng/ml and in children with diagnosed CVHC (n=20) – 111,29±5,39 ng/ml (p>0,05).

Also, we have determined the distribution of Arg-1 depending on sex, age peculiarities, degree of liver fibrosis and concomitant oncological diseases in clinical anamnesis (table 2).

It was established, that Arg-1 level in male representatives of study group (n=26; 110,46±6,11 ng/ml) was higher than in females (n=14; 105,08±8,46 ng/ml). The similar tendency was reported among children of control group. Also, Arg-1 level in patients of study group was significant higher that in patients of control group (table 2).

The peculiarities of distribution of the Arg-1 level depending on age also was performed in all enrolled patients of study and control groups (table 3).

It was reported, that in patients of study group (n=40) level of Arg-1 was increasing with age of patients (table 3). The same tendency was detected within

Table 1

Distribution of enrolled patients of study and control groups depending on sex and age (%)

Parameters	Study group (n=40)				Control group (n=20)	
	Patients with CVHB (n=20)		Patients with CVHC (n=20)			
	Abs.	%	Abs.	%	Abs.	%
Mean of age (years)	11,05±0,78		11,9±0,92		8,9±0,69	
Sex						
– male	7	35,0	7	35,0	12	60,0
– female	13	65,0	13	65,0	8	40,0
Age group						
– up to 6 years	3	15,0	-	-	3	15,0
– from 6 to 9 years	1	5,0	6	30,0	8	40,0
– from 9 to 17 years	16	80,0	14	70,0	9	45,0

Table 2

Arg-1 level in patients of study and control group depending on sex (M±m)

Laboratory index	Study group (n=40)		Control group (n=20)	
	Male (n=26)	Female (n=14)	Male (n=12)	Female (n=8)
Arginase-1, ng/ml	110,46±6,11*	105,08±8,46**	83,41±7,89	66,08±8,95

Note:

** – there is a significant difference between compared with control group at p<0,05;*

*** – there is a significant difference between compared with control group at p<0,01.*

Table 3

Arg-1 level in patients of study and control group depending on age (M±m)

Laboratory index	Study group (n=40)			Control group (n=20)		
	Up to 6 years (n=3)	6-9 years (n=7)	From 9 to 17 years (n=30)	Up to 6 years (n=3)	6-9 years (n=8)	From 9 to 17 years (n=9)
Arginase-1, ng/ml	98,2± 19,45	102,9± 10,71*	110,94± 5,85	51,54± 10,1	67,69± 6,79	92,52± 9,23

Note:

** – there is a significant difference between compared with control group at p<0,05.*

Table 4

Arg-1 level in patients of study and control group depending on liver fibrosis stage (M±m)

Laboratory index	Degree of liver fibrosis						Control group (n=20)
	F0 (n=16)	F0-1 (n=7)	F1 (n=2)	F1-2 (n=9)	F2 (n=1)	F3 (n=5)	
Arginase-1, ng/ml	124,07±7,7 ***	102,55± 14,03	106,55±0,15 ***	106,07±8,5 **	89,44 *	76,6±1,0	76,48±6,09

Note:

** – there is a significant difference between compared with control group at p<0,05;*

*** – there is a significant difference between compared with control group at p<0,01;*

**** – there is a significant difference between compared with control group at p<0,001.*

patients of control group. Should be noted, that Arg-1 level in children from 6 to 9 years of study group (n=7) was significant higher (102,9±10,71 ng/ml) compared with patients of control group (n=8; 67,69±6,79 ng/ml) (p<0,05).

In addition, we have determined peculiarities of the level of Arg-1 among children of study group (n=40) depending on concomitant oncological disease (in anamnesis). It was noted, that the level of Arg-1 in children of study group with concomitant oncological diseases (n=26) in remission stage was higher – 115,24±6,2 ng/ml, compared with children without this factor (n=14) –96,22±7,14 ng/ml.

Among children of study group (n=40) we have performed analysis of Arg-1 depending on degree of liver fibrosis according to Metavir scale (table 4).

After analysis of Arg-1 level distribution depended on liver fibrosis stage, it was established that level of Arg-1 was significant higher in patients with liver fibrosis F0 (124,07±7,7 ng/ml; p<0,001), F1 (106,55±0,15 ng/ml; p<0,001), F1-2 (106,07±8,5 ng/ml; p<0,01), F2 (89,44 ng/ml; p<0,05) compared with control group (76,48±6,09 ng/ml). It was noted, that among children of study group total level of Arg-1 was reducing with increasing of stage of liver fibrosis according to Metavir scale.

In addition, we have established correlation between Arg-1 level and degree of liver fibrosis. It was noted that between Arg-1 level and liver fibrosis stage according to Metavir scale was detected indirect significant correlation relation with moderate degree (R=-0,49; p=0,001).

Conclusions.

1. Researches for new markers of non-invasive laboratory diagnosis of liver fibrosis in children with chronic viral hepatitis B and C should be performed by scientists.
2. Arginase-1 (Arg-1) – important marker that should be studied by scientists nowadays to understand the pathogenesis of fibrogenesis of the liver.
3. In examined patients of study group (n=40) level of Arg-1 was significant higher (108,58±4,9 ng/ml) compared with patients of control group (n=20) – 76,48±6,09 ng/ml (p<0,001).
4. Arg-1 level in male representatives was higher in both groups of examined. Also, total level of Arg-1 among patients of study and control group increased with increasing of patients' age.
5. The level of Arg-1 in children of study group with concomitant oncological diseases was higher (115,24±6,2 ng/ml), compared with children without this factor (96,22±7,14 ng/ml).
6. Correlation relation between Arg-1 level and liver fibrosis degree was detected among patients of study group (R=-0,49; p=0,001).

Prospects for further research.

In further researches, 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 taking into account ranges and levels of FABP-1-L and YKL-40, as additional non-invasive laboratory markers of liver fibrosis.

References:

1. Lampertico, P., Agarwal, K., Berg, T., Buti, M., Janssen, H. L., Papatheodoridis, G., ... & Tacke, F. (2017). EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *Journal of hepatology*, *67*(2), 370–398.
2. Yapali, S., Talaat, N., & Lok, A. S. (2014). Management of hepatitis B: our practice and how it relates to the guidelines. *Clinical gastroenterology and hepatology*, *12*(1), 16–26.
3. Indolfi, G., Easterbrook, P., Dusheiko, G., El-Sayed, M. H., Jonas, M. M., Thorne, C., ... & Penazzato, M. (2019). Hepatitis C virus infection in children and adolescents. *The lancet Gastroenterology & hepatology*, *4*(6), 477–487.
4. Modin, L., Arshad, A., Wilkes, B., Benselin, J., Lloyd, C., Irving, W. L., & Kelly, D. A. (2019). Epidemiology and natural history of hepatitis C virus infection among children and young people. *Journal of hepatology*, *70*(3), 371–378..

5. Sun, Y., Wu, X., Zhou, J., Meng, T., Wang, B., Chen, S., ... & You, H. (2020). Persistent low level of hepatitis B virus promotes fibrosis progression during therapy. *Clinical Gastroenterology and Hepatology*, *18*(11), 2582–2591.
6. Deng, Y., Li, G., Chang, D., & Su, X. (2020). YKL-40 as a novel biomarker in cardio-metabolic disorders and inflammatory diseases. *Clinica Chimica Acta*, *511*, 40–46.
7. Tizaoui, K., Yang, J. W., Lee, K. H., Kim, J. H., Kim, M., Yoon, S., ... & Smith, L. (2022). The role of YKL-40 in the pathogenesis of autoimmune diseases: A comprehensive review. URL: https://ir.ymlib.yonsei.ac.kr/handle/22282913/188616
8. Guan, R., Lin, R., Jin, R., Lu, L., Liu, X., Hu, S., & Sun, L. (2020). Chitinase-like protein YKL-40 regulates human bronchial epithelial cells proliferation, apoptosis, and migration through TGF-β1/Smads pathway. *Human & Experimental Toxicology*, *39*(4), 451–463.
9. Zhang, Z., Wang, H., Yan, Z., & Zhu, K. (2022). Up-regulated YKL-40 is associated with poor prognosis of hepatocellular carcinoma patients with hepatitis B-related cirrhosis. *Archives of Medical Science*. DOI: https://doi.org/10.5114/aoms/141821
10. Bielawski, K., Rhone, P., Bulsa, M., & Ruszkowska-Ciastek, B. (2020). Pre-operative combination of normal BMI with elevated YKL-40 and leptin but lower adiponectin level is linked to a higher risk of breast cancer relapse: A report of four-year follow-up study. *Journal of Clinical Medicine*, *9*(6), 1742.
11. Wang, J., Qi, S., Zhu, Y. B., & Ding, L. (2022). Prognostic value of YKL-40 in colorectal carcinoma patients: A meta-analysis. *World Journal of Clinical Cases*, *10*(7), 2184.
12. Yamamoto N, Sugimoto K, Murata K, Nakano T. Noninvasive estimation of liver fibrosis and response to interferon therapy by a serum fibrogenesis marker, YKL-40, in patients with HCVassociated liver disease. World J Gastroenterol 2005; 11(4): 476–481 http://www.wjgnet.com/1007-9327/11/476.asp
13. Del Turco, S., De Simone, P., Ghinolfi, D., Gaggini, M., & Basta, G. (2021). Comparison between galectin-3 and YKL-40 levels for the assessment of liver fibrosis in cirrhotic patients. *Arab Journal of Gastroenterology*, *22*(3), 187–192.
14. Kwon Y, Kim JH, Ha EK, Jee HM, Baek HS, Han MY, Jeong SJ. Serum YKL-40 Levels Are Associated with the Atherogenic Index of Plasma in Children. Mediators Inflamm. 2020 Sep 26;2020:8713908. doi: 10.1155/2020/8713908. PMID: 33061832; PMCID: PMC7533750
15. Milner, K.-L., van der Poorten, D., Xu, A., Bugianesi, E., Kench, J.G., Lam, K.S.L., Chisholm, D.J. and George, J. (2009), Adipocyte fatty acid binding protein levels relate to inflammation and fibrosis in nonalcoholic fatty liver disease. Hepatology, 49: 1926–1934. https://doi.org/10.1002/hep.22896
16. Li, H.-L., Wu, X., Xu, A., & Hoo, R. L.-C. (2021). A-FABP in Metabolic Diseases and the Therapeutic Implications: An Update. International Journal of Molecular Sciences, 22(17), 9386. https://doi.org/10.3390/ijms22179386
17. Pillai, S. S., Lakhani, H. V., Zehra, M., Wang, J., Dilip, A., Puri, N., ... & Sodhi, K. (2020). Predicting nonalcoholic fatty liver disease through a panel of plasma biomarkers and microRNAs in female West Virginia population. *International Journal of Molecular Sciences*, *21*(18), 6698
18. Rakela, J. L., Karvellas, C. J., Koch, D. G., Vegunta, S., & Lee, W. M. (2023). Acute Liver Failure: Biomarkers Evaluated by the Acute Liver Failure Study Group. *Clinical and Translational Gastroenterology*, *14*(4).
19. Watt, J., Kurth, M. J., Reid, C. N., Lamont, J. V., Fitzgerald, P., & Ruddock, M. W. (2022). Non-alcoholic fatty liver disease – A pilot study investigating early inflammatory and fibrotic biomarkers of NAFLD with alcoholic liver disease. *Frontiers in Physiology*, *13*, 963513
20. Eguchi, A., & Iwasa, M. (2021). The role of elevated liver-type fatty acid-binding proteins in liver diseases. *Pharmaceutical Research*, *38*, 89–95.
21. Pesce JT, Ramalingam TR, Mentink-Kane MM, Wilson MS, El Kasmi KC, et al. (2009) Arginase-1–Expressing Macrophages Suppress Th2 Cytokine–Driven Inflammation and Fibrosis. PLoS Pathog 5(4): e1000371. doi:10.1371/journal.ppat.1000371
22. Kitowska, K., Zakrzewicz, D., Konigshoff, M., Chrobak, I., Grimminger, F., Seeger, W., ... & Eickelberg, O. (2008). Functional role and species-specific contribution of arginases in pulmonary fibrosis. *American Journal of Physiology-Lung Cellular and Molecular Physiology*, *294*(1), L34–L45.
23. Chrzanowska, A., Gajewska, B., & Barańczyk-Kuźma, A. (2009). Arginase isoenzymes in human cirrhotic liver. Acta Biochimica Polonica, 56(3), 465–469.