et al. *JAMA Netw Open*. 2019. Vol. 2, No. 12. e1916769. DOI: https://doi.org/10.1001/jamanetworkopen.2019.16769

15. The impact of pneumococcal vaccination on bacterial and viral pneumonia in Western Australian children: record linkage cohort study of 469,589 births (1996-2012) / P. Fathima, et al. *Clin Infect Dis*. 2017. Oct 23. Medline. DOI: https://doi.org/10.1093/cid/cix923

The article was received
2019.11.06

UDC 616.36-006.327-074:616.366-002.2:613.25 https://doi.org/10.26641/2307-0404.2020.1.200403

A.Yu. Filippova

DIAGNOSTICS OF THE PROGRESSION OF LIVER FIBROSIS IN PATIENTS WITH NON-ALCOHOLIC STEATOHEPATITIS IN COMBINATION WITH OBESITY AND CHRONIC CALCULOUS CHOLECYSTITIS

SE «Dnipropetrovsk medical academy of Health Ministry of Ukraine»
Department of Internal Medicine 2 and phthisiology
V. Vernadsky str., 9, Dnipro, 49044, Ukraine
ДЗ «Дніпропетровська медична академія МОЗ України»
кафедра внутрішньої медицини 2 і фтизіатрії
(зав. – д. мед. н., проф. О.В. Курята)
вул. В. Вернадського, 9, Дніпро, 49044, Україна
e-mail:Filippova-dma@i.ua

Цитування: Медичні перспективи. 2020. Т. 25, № 1. С. 65-73
Cited: Medicni perspektivi. 2020;25(1):65-73

Key words: *nonalcoholic steatohepatitis, obesity, fibrosis, histological diagnostics*
Ключові слова: *неалкогольний стеатогепатит, ожиріння, фіброз, гістологічна діагностика*
Ключевые слова: *неалкогольный стеатогепатит, ожирение, фиброз, гистологическая диагностика*

Abstract. Diagnostics of the progression of liver fibrosis in patients with non-alcoholic steatohepatitis in combination with obesity and chronic calculous cholecystitis. Filippova A.Yu. *The aim of the work is to investigate the diagnostic value of laboratory blood biomarkers – alanine aminotransferase, aspartate aminotransferase, oxyproline and prothrombin time in comparison with morphological indicators for diagnosis of the degree of liver fibrosis in patients with comorbid course of non-alcoholic steatohepatitis (NASH) in combination with obesity and chronic calculous cholecystitis. The data of 22 patients with NASH in combination with obesity and chronic calculous cholecystitis was analyzed by laboratory and morphological indicators. There were 6 (27.2%) men and 16 (72.8%) women among the patients. Liver biopsy was performed intra-operatively on performing surgical treatment of calculus cholecystitis. METAVIR and E. Brunt criteria were used in the histological diagnosis of NASH, as well as for determination of the stage of liver fibrosis (LF). Hepatic tissue fibrogenesis was assessed by serum values of total (OPT), free (OPF) and protein-bound (OPB) oxyproline, activity of indirect fibrosis markers – alanine aminotransferase (ALT), aspartate aminotransferase (AST), AST/ALT ratio and prothrombin time (PTT). As a mathematical tool for modeling, stepwise discriminant analysis was used. Fibrosis of the first stage (F1) was observed in 5 (22.7%)*

patients, the second stage of fibrosis (F2) – in 7 (31.8%), F3 stage of fibrosis – in 10 (45.5%) patients. Analysis of the morphological study of liver biopsy samples in examined patients with NASH indicates that established histological changes combine the signs of fatty and protein degeneration of hepatocytes, inflammation and necrosis in the lobules. Among the indicators included in the mathematical model the highest diagnostic significance can be attributed to the AST / ALT ratio (F=9.03; p=0.003) and the level of OPF (F=5.67; p=0.016), whereas OPB level has the lowest value (F=2.94; p=0.086). Evaluation of the accuracy of the method for determining of the LF phase based on the proposed algorithm showed that the frequency of correct detecting of F1 and F2 stages of LF was 100%, for the F3 stage – 90% (1 case attributed to the F2 stage). In general, the accuracy of the method was 95.5% (95% CI 86.8-100%), sensitivity – 90.0% (95% CI 71.4-100%), specificity – 100% (95% CI 92.5-100%), validity – 90.0%. Evaluation of the stage of LF in patients with NASH in combination with obesity and chronic calculous cholecystitis, which was determined using discriminant functions calculated from laboratory data (OPT, OPF, OPB, ALT, AST/ALT ratio and PTT), is very much in line with the corresponding results of histopathological studies of liver biopsy samples.

Реферат. Диагностика прогрессирования фиброза печени у больных с неалкогольным стеатогепатитом в сочетании с ожирением и хроническим калькулезным холециститом. Филиппова А.Ю. *Цель работы – определить диагностическую ценность лабораторных биомаркеров крови – аланинаминотрансферазы, аспартатаминотрансферазы, оксипролинов и протромбинового времени в сравнении с морфологическими показателями для диагностики степени выраженности фиброза печени у больных с неалкогольным стеатогепатитом (НАСГ) в сочетании с ожирением и хроническим калькулезным холециститом. По лабораторным и морфологическим показателям проанализированы данные 22 больных с НАСГ в сочетании с ожирением и хроническим калькулезным холециститом. Среди больных было 6 (27,2%) мужчин и 16 (72,8%) женщин. Биопсия печени проводилась интраоперационно, при выполнении хирургического лечения калькулезного холецистита. В гистологической диагностике НАСГ, а также для определения стадии фиброза печени (ФП) использовали критерии METAVIR и E. Brunt. Процессы фиброгенеза печеночной ткани оценивали в сыворотке крови по содержанию оксипролинов общего (ОПО), свободного (ОПС) и белковосвязанного (ОПБ), активности косвенных маркеров фиброза – аланинаминотрансферазы (АлАТ), аспартатаминотрансферазы (АсАТ), соотношения АсАТ/АлАТ и протромбинового времени (ПТВ). В качестве математического инструмента для моделирования использовали пошаговый дискриминантный анализ. Фиброз первой стадии (F1) наблюдался у 5 (22,7%) больных, вторая стадия фиброза (F2) – у 7 (31,8%), F3 стадия фиброза – у 10 (45,5%) больных. Анализ морфологического исследования биоптатов печени у обследованных больных с НАСГ указывает на то, что установленные гистологические изменения объединяют признаки жировой и белковой дистрофии гепатоцитов, воспаления и некроза в дольках. Среди включенных в математическую модель показателей наибольшую диагностическую значимость имели соотношение АсАТ / АлАТ (F=9,03; p=0,003) и уровень ОПС (F=5,67; p=0,016), наименьшую – уровень ОПБ (F=2,94; p=0,086). Оценка показателей точности метода определения стадии ФП по предложенному алгоритму показала, что частота правильного выявления F1 и F2 стадий ФП составила 100%, для F3 стадии – 90% (1 случай отнесен к F2 стадии). В целом, точность метода составила 95,5% (95% ДИ 86,8-100%), чувствительность – 90,0% (95% ДИ 71,4-100%), специфичность – 100% (95% ДИ 92,5-100%), валидность – 90,0%. Оценка стадии ФП у больных с НАСГ в сочетании с ожирением и хроническим калькулезным холециститом, определенная с помощью дискриминантных функций, рассчитанных по данным лабораторных показателей (ОПО, ОПС, ОПБ, АлАТ, АсАТ/АлАТ и ПТВ), хорошо согласуется с соответствующими результатами гистопатологического исследования биоптатов печени.*

Non-alcoholic fatty liver disease (NAFLD) is the most common diffuse pathology of the hepatobiliary system and one of the most studied problems worldwide [7, 11, 13, 14]. According to recent data, the prevalence of NAFLD in Western Europe is 20-30%, in Asia - 15%, in the USA about 40% of the population suffer from NAFLD and about 25% of those ones have progressive inflammatory liver disease - non-alcoholic steatohepatitis (NASH) [15]. As for today, the final diagnosis of NASH is established on the basis of histological evidence not only regarding the presence of increased fat in hepatocytes, but also due to damage to cells, necrotic changes and subsequent formation of fibrosis [3, 12]. Liver fibrosis (LF) accompanies all chronic diffuse liver diseases and is a reliable sign of progression of organ damage. This is precisely why determining the stage of fibrosis is prognostically significant and is used in clinical practice as one of the important criteria for determining the tactics of managing patients, which is especially true in chronic hepatitis of different genesis [3, 4, 9, 16]. Limited possibilities of early diagnosis, complexity of pathogenesis and questions concerning features of formation and progression of the reactions leading to fibrosis depending on the concomitant factors, comorbid background make considerable difficulties in choosing the optimal complex of therapeutic measures. The relevance of the diagnosis of liver fibrosis increases with the appearance of the number

Licensed under CC BY 4.0

of evidence of its reversibility [16]. The first method to evaluate the stage of fibrosis is biopsy. The disadvantages inherent in the morphological method of the study, especially its invasiveness have given impetus to the development and implementation of non-invasive methods of diagnosis in clinical practice, which allow with sufficient degree of reliability to determine the stage of liver disease, to carry out dynamic observation and evaluate the efficacy.

Further search for new non-invasive and highly informative methods for evaluating LF as one of the major criteria for disease progression is of major clinical importance. Among the non-invasive methods at the first level of diagnosis are laboratory findings of fibrosis [2]. They are divided into direct that reflect the amount of fibrotic tissue, and indirect, reflecting the activity of the inflammatory process and damage to the parenchyma, its impaired synthetic function, allowing further evidence of the presence and severity of LF, which may include laboratory findings of liver tests [4, 16]. Based on a combination of indirect laboratory biomarkers of fibrosis, more than 20 different indices and scales for the diagnosis of LF have been proposed.

Search for safe, available and effective methods for evaluating LF remains an urgent problem in internal medicine. Therefore, today in-depth research with mathematical modeling of the progression of reactions leading to fibrosis in patients with comorbid NASH is an urgent need that determines the direction of study and in further opens the way to a real improvement in the treatment outcomes of this category of patients.

The aim of the work is to determine the diagnostic value of laboratory biomarkers of blood – alanine aminotransferase, aspartate aminotransferase, oxyproline and prothrombin time in comparison with morphological indicators for the diagnosis of the degree of liver fibrosis in patients with NASH combined with chronic calculous cholecystitis.

MATERIALS AND METHODS OF RESEARCH

To create mathematical models for the evaluation of the stage of LF development in patients with NASH combined with obesity (OB) and chronic calculous cholecystitis (HCC), laboratory findings and morphological parameters of 22 patients with NASH were analyzed. All patients enrolled in the study were treated at the surgical department of the State Establishment “Institution of Gastroenterology of the National Academy of Medical Sciences of Ukraine” because of exacerbation of chronic calculous cholecystitis. Among the patients there were 6 (27.2%) men and 16 (72.8%) women. The mean age of the patients was 53.3±1.28 years.

The diagnosis of NAFD OB and HCC was established in accordance with the global practical guidelines of the World Gastroenterology Organization of 2013 WGO Global Guideline Obesity, standardized protocols for the diagnosis and treatment of digestive diseases in accordance with the Order of the Ministry of Health of Uukraine No. 271 of 13.06.2005, unified clinical protocol of primary, secondary (specialized) medical care “Non-alcoholic steatohepatitis”, Order of the Ministry of Health of Ukraine No. 826 of 06.08.2014, ICD-10. Exclusion criteria for the study were: data on alcohol abuse (consumption of more than 50 g of ethanol/week for men, more than 30 g of ethanol/week for women during the last year), the presence of signs of chronic viral, autoimmune and drug hepatitis; acute viral hepatitis during the last year; presence of reliable signs of other diffuse liver diseases; absence of liver fibrosis according to morphological study, presence of concomitant diseases in the stage of decompensation; verified diabetes mellitus type I and II, BMI >40 kg/m^2. All patients enrolled in the study underwent a standard general clinical study (clinical blood and urine tests, liver complex – to detect exacerbation of pathological process and signs of cytolysis). Height and waist measurement (WM) on an empty stomach was performed, hip width (HW) and body weigh were determined. To determine the nature of the distribution of fat in the body, the ratio of WM/HW was used. Obesity was considered abdominal if WM was >94 cm for men and >80 cm for women, WM/HW – >0.88 for women, and 0.9 – for men. Body mass index (BMI) was determined by the Kettle formula. The average BMI in the studied patients was 32.55±0.71 kg/m^2.

Before to laparoscopic cholecystectomy, all patients underwent ultrasound examination of the abdominal cavity. Liver biopsy was performed after obtaining informed consent of the patient for surgery, which was reflected in the record No. 2 of the meeting of the committee on biomedical ethics of the State Establishment "Dnipropetrovsk medical academy of the Ministry of Health of Ukraine" of 25.10.2017. Liver biopsy was performed intraoperatively (during the surgical treatment of calculous cholecystitis – laparoscopic cholecystectomy). An indication for laparoscopic cholecystectomy was exacerbation of chronic calculous cholecystitis in patients with NASH and OB. In each patient liver three biopsy slides from different areas of the liver (V, VII segments) were taken. The material was fixed in Bouin's solution overnight at a room temperature. Then it was held in a series of alcohols of ascending strength through a mixture of alcohol

and chloroform, paraffin "porridge", and was enclosed in paraffin. Thin histological sections, 5 μm thick, were obtained using a rotary microtome. For histological examination, sections were stained with hematoxylin and eosin according to the Mallory-Slinchenko method. The state of the histological structure of the liver was evaluated semi-quantitatively in the system of degrees (0 – no changes, 1 – mild degree of 3-5%, 2 – moderate degree, 3 – expressed degree of 60-100%), type of cholestasis, degree of chronic inflammation, degree of protein and fatty dystrophy. Histological preparations were studied with the help of the light microscope "LUMAM-I2".

The METAVIR and E. Brunt criteria were used in histological diagnosis of NASH and to determine the stage of LF [8, 10]. According to the conventional METAVIR scale, in patients with F1 stage fibrosis, distension of portal tracts was observed without septa formation, portal fibrosis in combination with single septa was revealed in F2 stage, portal fibrosis in combination with multiple septa without formation of pseudo acini – in F3 stage.

In the diagnosis of liver steatosis macrovesicular, microvesicular and mixed forms were distinguished. The severity of steatosis was determined by the involvement of liver acini in steatosis: mild steatosis (part of the perivenular zone), moderate steatosis (the entire perivenular zone) and pronounced (covering two or three zones of the liver acini).

The processes of fibrogenesis of the liver tissue were evaluated by the content of oxyproline total (OPT), oxyproline free (OPF), oxyproline protein bound (OPB) in serum, activity of indirect markers of fibrosis – alanine aminotransferase (AlAT), aspartate aminotransferase (AAT), ratio of AlAT/AAT, absolute platelet count and prothrombin time (PTT). In the blood, the content of OPT, OPF and OPB was investigated by Osadchuk, the activity of AlALT, AAT – by the method of Reitman- Frenkel. PTT evaluation was performed by the time of plasma fibrin clot formation when calcium chloride and thromboplastin were added to it. PTT values were presented in seconds, indicating the control values obtained in the study of control normal plasma [2].

Statistical processing of the study materials was performed using biostatistics methods implemented in the STATISTICA v.6.1 (Statsoft Inc., USA) licensed software package (license number AGAR909E415822FA). Discriminant Function Analysis was performed to differentiate the degree of fibrosis in NASH according to laboratory data. The discriminant analysis algorithm involved the formation of a training sample, the execution of a step-by-step procedure (forward stepwise) selection of the most informative indicators, the creation of decisive rules in the form of linear discriminant functions (G), which maximize the differences between classes:

$$Gj = b0 + b1 \cdot x1 + ... + bm \cdot xm,$$

where Gj is a function for j of the differentiation class, b0 is a constant, b1, b2 ... bm are coefficients for the individual indices x1, x2 ... xm; x1, x2 ... xm - the value of the indicator in a particular patient, m – the number of selected informative indicators. Patients are referred to the class for which the calculated value of G has reached the maximum value.

The informative value of the features and the adequacy of the model were evaluated according to the criteria of Fisher (F) and Wilk's, the quality of the developed decisive rules - by comparing the classification results with the initial classification in the training sample with the calculation of indicators of sensitivity and specificity [1].

RESULTS AND DISCUSSION

According to the results obtained, signs of fatty dystrophy of hepatocytes among patients with NASH developed on the basis of OB and chronic calculous cholecystitis: in 10 (45.4%) patients they were of macrovesicular, in 6 (27.3%) patients – of microvesicular, in 6 (27.3%) – of mixed type, which is mainly localized in zone 3 by Rappoport (Table).

In the examination of histological material, first stage (F1) fibrosis was observed in 5 (22.7%) patients: mild – in 2 (9.1%) and moderate – in 3 (13.6%) patients with steatosis; the second stage of fibrosis (F2) – in 7 (31.8%) patients: of them in 6 (27.3%) – moderate degree of steatosis and in 1 (4.5%) patient – expressed; F3 stage of fibrosis – in 10 (45.5%) patients: of them in 4 (18.2%) – moderate degree of steatosis and in 6 (27.3%) patients – expressed with the formation of incomplete and complete fibrotic septa (Fig. 1, Fig. 2, Table).

According to the evaluation of the stage of liver fibrosis by criteria of E. Brunt in comorbid patients with NASH in 1 stage of fibrosis (F1) pericellular LF, mainly focal (80,0%) was revealed. In stage 2 (F2) fibrosis, focal (28.6%) and predominantly periportal and portal fibrosis (71.4%) was recorded. In stage 3 (F3) liver fibrosis, in all patients the formation of portocentral septa occurred.

Analysis of the morphological study of liver biopsy samples in the examined patients with NASH also indicates that the established histological changes combine the signs of fatty and protein dystrophy of hepatocytes, inflammation, necrosis, apoptosis in the acini. In 100.0% of patients with NASH, granular protein dystrophy of hepatocytes was found, which was mostly diffuse.

Licensed under CC BY 4.0

Table$

Morphologic types and stages of liver steatosis in patients with NASH (abs./%)

Patients	Type of liver steatosis			Stage of liver steatosis		
	macrovesicular	microvesicular	mixed	mild ≤33%	moderate >33-66%	expressed >66%
NASH, n=22	10/ 45,4	6/ 27,3	6/ 27,3	2/9,1	13/59,1	7/31,8

Findings of biochemical profile, which are considered to be indirect markers of fibrosis (AlAT, AAT/AlAT ratio, absolute platelet count, PTT), as well as connective tissue metabolism indicators (OPT, OPB, OPF) were selected as independent predictors in the first stage. Stepwise discriminant analysis was used as a mathematical modeling tool. Using the procedure Forward stepwise allowed to exclude an indicator of the absolute number of platelets from the model, which is weakly correlated with the stage of fibrosis (F=0.66; p=0.535). Among the findings included in the model, the greatest diagnostic significance was the ratio of AAT/ AlAT (F=9.03; p=0.003) and the level of OPF (F=5.67; p=0.016), the lowest – the level of OPB (F=2.94; p=0.086).

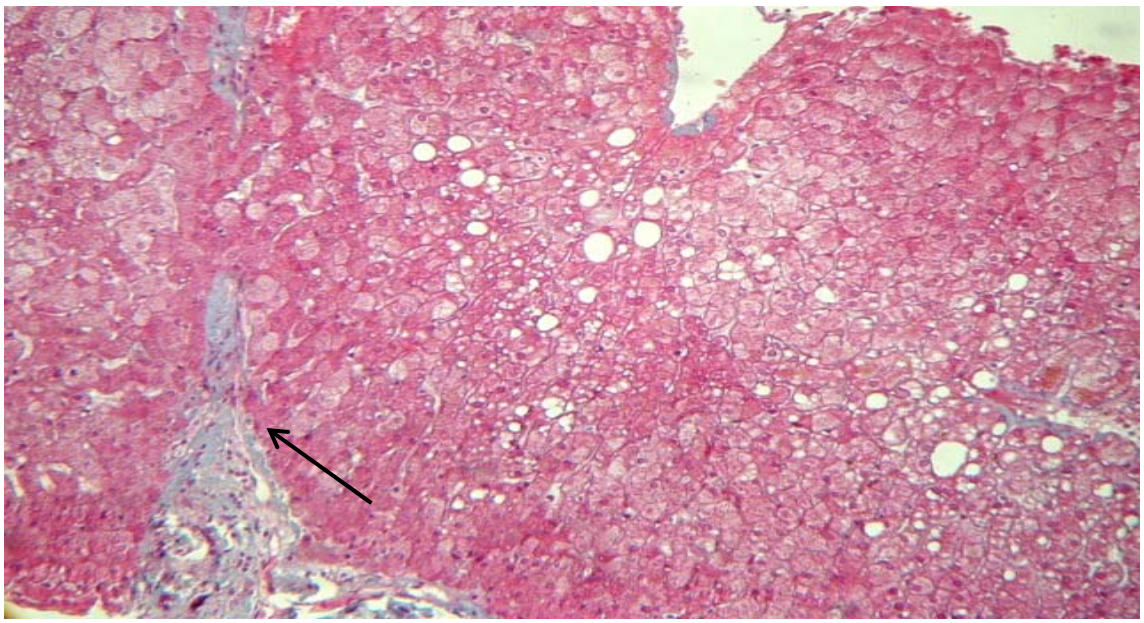

Fig. 1. NASH in patient with OB st. II. Incomplete fibrotic septa in liver parenchyma (indicated by arrow). Staining by Mallory in modification of M.Z. Slinchenko x100

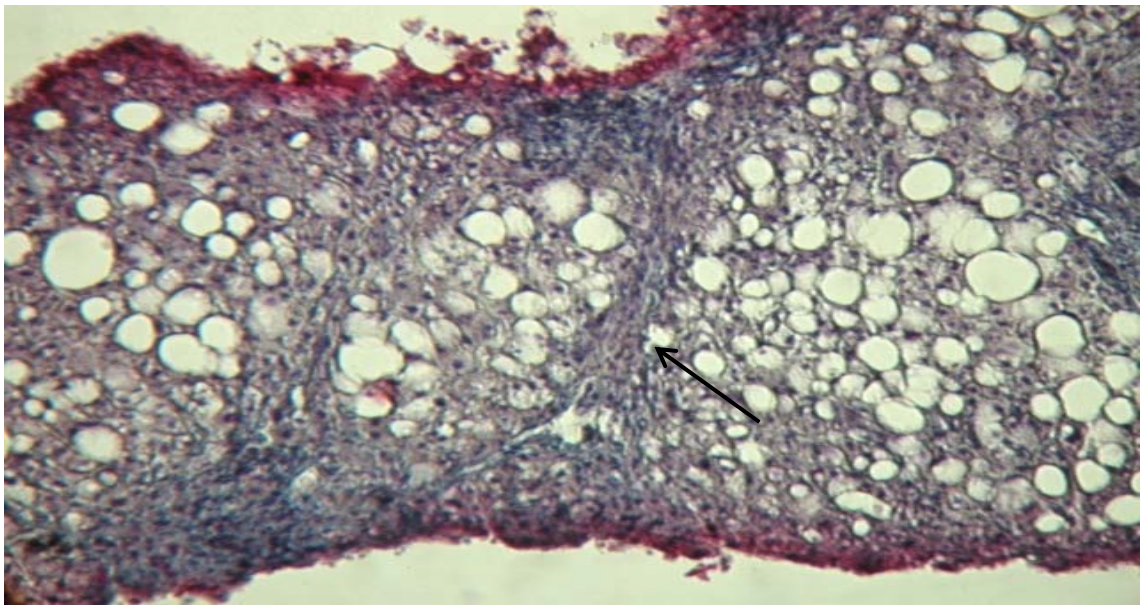

Fig. 2. NASH in patient with OB st. II. Macrovesicular steatosis of liver 90% of area (III st.). Complete fibrotic septa in liver parenchyma (indicated by arrow). Staining by Mallory in modification of M.Z. Slinchenko x100

The following discriminant functions are calculated:

G1=[AAT / AlAT x 64.06-
AlAT x 6.55+OPF x 1.75+OPT x 0.79+OPB x
x 0.034+PTT x 5.56]-121.66
G2=[AAT / AlAT x 38.33-
AlAT x 5.68+OPF x 1.43+OPT x 0.51+OPB x
x 0.029+PTT x 5.0]-78.99
G3=[AAT / AlAT x 52.04-
AlAT x 1.56+OPF x 1.2+OPT x 0.69+OPB x
x 0.023+PTT x 4.42]-79.75,

where G1 - discriminant function characteristic of the first stage (F1) of fibrosis;
G2 – discriminant function that determines the second stage (F2);
G3 – discriminant function characteristic of the third stage of fibrosis (F3);
units of measurement of findings: AAT mmol/L, ALT mmol/L, OPF mmol/L, OPT mmol/L, OPB mmol/L, PTT %.

The stage of LF in patients with NASH was determined by the maximum value of the discriminant function:

- at G1>G2 and G1>G3 F1 stage was determined;

- at G2>G1 and G2>G3 - F2 stage;

- at G3>G1 and G3>G2 - F3 stage.

The constructed mathematical model corresponded to the initial data according to Wilk's criteria W=0.133, Fisher F=4.07 at p=0.001. The evaluation of the accuracy of the method of detection of the LF stage by the proposed algorithm showed that the frequency of correct establishment of F1 and F2 stages of the LF was 100%, for F3 stage – 90% (1 case was attributed to F2 stage) (Fig. 3). In sum, the accuracy of the method was 95.5% (95% CI 86.8-100%), sensitivity - 90.0% (95% CI 71.4-100%), specificity - 100% (95% CI 92.5-100%), validity – 90.0%.

In recent years, there have been an increasing number of studies evaluating the possible impact of various factors on key links in fibrogenesis, the course and consequences of liver disease [3, 5, 14, 16]. Studies that compared the results of the study with the corresponding results of histopathological examination of liver samples found similar trends in patients with chronic diffuse liver disease [4]. However, the presented study in patients with non-alcoholic steatohepatitis on the background of obesity and chronic calculous cholecystitis was perfo-rmed for the first time using laboratory and morphological markers of fibrosis.

Liver biopsy is an accurate method of diagnosis of diffuse liver disease, namely steatohepatitis [3, 10]. For the diagnosis of differences between stages of liver fibrosis, this method is the most informative, which allows to estimate the risk of disease progression to the stage of steatohepatitis [3]. The results of the discriminant analysis on the evaluation of the stage of LF formation in patients with a comorbid course of NASH by laboratory findings is a non-invasive and at the same time highly informative method. The use of discriminant analysis for the diagnosis of LF according to laboratory findings of OPF, OPB, OPT, AlAT, AAT/ ALAT, PTT in patients with NASH against the background of obesity allows to assess the risk of disease progression in increase of LF stage.

Licensed under CC BY 4.0

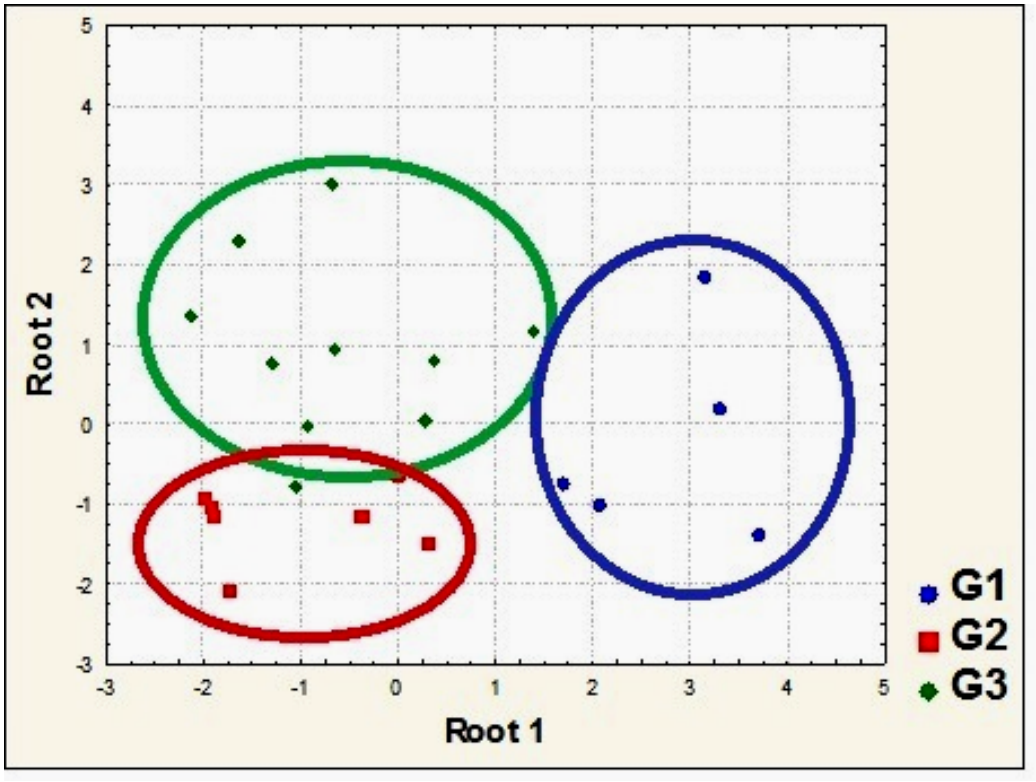

Fig. 3. Results of discriminant analysis evaluating stages of LF development in patients with NASH according to laboratory findings

CONCLUSIONS

1. The assessment of LF stage in patients with NASH combined with obesity and chronic calculous cholecystitis was determined using discriminant functions calculated according to laboratory findings, it is well compliant with the relevant results of histopathological examination of liver biopsy samples. The accuracy of the method was 95.5% (95% CI 86.8-100%), sensitivity – 90.0% (95% CI 71.4-100%), specificity – 100% (95% CI 92.5-100 %), validity – 90.0%.

2. The application of such an algorithm in practice will make it with high probability to evaluate the stage of LF by the available biochemical findings and to use this information to dynamically monitor the intensity of fibrosis and timely correction of therapy in patients with NASH combined with obesity and chronic calculous cholecystitis.

The prospect of further research is to identify risk factors for the creation of mathematical models for predicting the course of non-alcoholic steatohepatitis in patients with comorbid pathology.

REFERENCES

1. Antomonov MYu. [Mathematical processing and analysis of biomedical data]. 2nd ed. Kyiv: MITS «Medinform»; 2018. p. 576. Ukrainian.

2. Kamyshnikov VS. [Clinical and laboratory diagnosis of liver diseases]. 3nd ed. Moskva: MEDpress-inform; 2019. p. 96. Russian.

3. Stepanov YuM., Filippova OYu. [Morphological basis for the assessment of steatosis, steatohepatitis and fibrosis in patients with nonalcoholic fatty liver disease in combination with obesity and pathology of the biliary tract]. Hastroenterolohiia. 2017;51(3):196-204. Ukrainian. doi: https://doi.org/10.22141/2308-2097.51.3.2017.112636

4. Filippova OYu. [Changes in direct markers of liver fibrosis in patients with steatohepatitis non-alcoholic and alcoholic origin on the background of obesity and pathology of the biliary tract]. Zaporizh. med. zhurnal. 2017;2(101):168-71. Ukrainian.
doi: https://doi.org/10.14739/2310-1210

5. Filippova OYu, Hubar IO. [Criteria for the forecasting of the disease of nonalcoholic steatohepatitis in patients with obesity and pathology of the biliary tract]. Svit medytsyny ta biolohii. 2017;4(62):99-103. Ukrainian. doi: https://doi.org/10.26724/2079-8334-2017-4-62-99-104

6. Filippova OYu, Hubar IO, Rudakova VV. [Prediction of the flow and progression of nonalcoholic fatty liver disease in patients with obesity and pathology of the biliary tract with the help of mathematical modeling]. Medicni perspektivi. 2017:22(4):74-80. Ukrainian. doi: https://doi.org/10.26641/2307-0404.2017.4.117674.

7. Ahmed A, Wong RJ, Harrison SA. Nonalcoholic Fatty Liver Disease Review: Diagnosis, Treatment, and Outcomes. Clin Gastroenterol Hepatol. 2015;13(12):2062-70. doi: https://doi.org/10.1016/j.cgh.2015.07.029

8. Bedossa P, Poynard T. An algorhythm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology. 1996;24(2):289-93. doi: https://doi.org/10.1002/hep.510240201

9. Gu Z, Li D, He H. Body mass index, waist circumference, and waist-to-height ratio for prediction of multiple metabolic risk factors in Chinese elderly population. Sci Rep. 2018;8(1):385.
doi: https://doi.org/10.1038/s41598-017-18854-1

10. Brunt EM, Neuschwander-Tetri BA, Oliver D. Nonalcoholic steatohepatitis: histologic features and clinical correlations with 30 blinded biopsy specimens. Hum. Pathol. 2004;35(9):1070-1082. doi: https://doi.org/10.1016/j.humpath.2004.04.017

11. Carr RM, Oranu A, Khungar V. Nonalcoholic Fatty Liver Disease: Pathophysiology and Management. Gastroenterol Clin North Am. 2016;45(4):639-52. doi: https://doi.org/10.1016/j.gtc.2016.07.003

12. Dietrich P, Hellerbrand C. Non-alcoholic fatty liver disease, obesity and the metabolic syndrome. Best Practice & Research Clinical Gastroenterology. 2014;28(4):637-53. doi: https://doi.org/10.1016/j.bpg.2014.07.008

13. El-Kader SMA. Non-alcoholic fatty liver disease: The diagnosis and management. World Journal of Hepatology. 2015;7(6):846-58.
doi: https://doi.org/10.4254/wjh.v7.i6.846

14. Filippova A. Non-alcoholic steatohepatitis in patients with obesity: interconnection between body mass, changes of lipid metabolism and concomitant pathology of biliary tract. EUREKA: Health Sciences. 2016;4:3-11. doi: https://doi.org/10.21303/2504-5679.2016.00115

15. Younossi Z, Anstee QM, Marietti M. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol. 2018;15(1):11-20.
doi: https://doi.org/10.1038/nrgastro.2017.109

16. Zhang CY, Yuan WG, He P. Liver fibrosis and hepatic stellate cells: Etiology, pathological hallmarks and therapeutic targets. World J Gastroenterol. 2016;22(48):10512-22. doi: https://doi.org/10.3748/wjg.v22.i48.10512

СПИСОК ЛІТЕРАТУРИ

1. Антомонов М. Ю. Математическая обработка и анализ медико-биологических данных. 2-е изд. Київ: МИЦ «Мединформ», 2018. 576 с.

2. Камышников В. С. Клинико-лабораторная диагностика заболеваний печени. 3-е изд. Москва: МЕДпресс-информ, 2019. 96 с.

3. Степанов Ю. М., Філіппова О. Ю. Морфологічні основи оцінки стеатозу, стеатогепатиту та фіброзу у хворих на неалкогольну жирову хворобу печінки у поєднанні з ожирінням і патологією біліарного тракту. *Гастроентерологія.* 2017. Т. 51, № 3. С. 196-204. DOI: https://doi.org/10.22141/2308-2097.51.3.2017.112636

4. Філіппова О. Ю. Зміни прямих маркерів фіброзу печінки у хворих з стеатогепатитами неалкогольного та алкогольного генезу на тлі ожиріння і патології біліарного тракту. *Запоріж. мед. журнал.* 2017. Т. 19, № 2. С. 168-171. DOI: https://doi.org/10.14739/2310-1210

5. Філіппова О. Ю., Губар І. О. Критерії прогнозування перебігу неалкогольного стеатогепатиту у хворих з ожирінням і патологією біліарного тракту. *Світ медицини та біології.* 2017. Т. 62. № 4. С. 99-103. DOI: https://doi.org/10.26724/2079-8334-2017-4-62-99-104

6. Філіппова О. Ю., Губарь І. О., Рудакова В. В. Прогнозування перебігу і прогресування неалкогольної жирової хвороби печінки у хворих з ожирінням і патологією біліарного тракту за допомогою математичного моделювання. *Медичні перспективи.* 2017. Т. XXII, № 4. С. 74-80. DOI: https://doi.org/10.26641/2307-0404.2017.4.117674

7. Ahmed A., Wong R. J., Harrison S. A. Nonalcoholic Fatty Liver Disease Review: Diagnosis, Treatment, and Outcomes. *Clin Gastroenterol Hepatol.* 2015. Vol. 13, No. 12. P. 2062-2070.
DOI: https://doi.org/10.1016/j.cgh.2015.07.029

8. Bedossa P., Poynard T. An algorhythm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. *Hepatology.* 1996. Vol. 24, No. 2. P. 289-293.
DOI: https://doi.org/10.1002/hep.510240201

9. Body mass index, waist circumference, and waist-to-height ratio for prediction of multiple metabolic risk factors in Chinese elderly population / Z. Gu, et al. *Sci Rep*. 2018. Vol. 8, No. 1. P. 385. DOI: https://doi.org/10.1038/s41598-017-18854-1

10. Brunt E. M., Neuschwander-Tetri B. A., Oliver D. Nonalcoholic steatohepatitis: histologic features and clinical correlations with 30 blinded biopsy specimens. *Hum. Pathol*. 2004. Vol. 35, No. 9. P. 1070-1082. DOI: https://doi.org/10.1016/j.humpath.2004.04.017

11. Carr R. M., Oranu A., Khungar V. Nonalcoholic Fatty Liver Disease: Pathophysiology and Management. *Gastroenterol Clin North Am*. 2016. Vol. 45, No. 4. P. 639-652. DOI: https://doi.org/10.1016/j.gtc.2016.07.003

12. Dietrich P., Hellerbrand C. Non-alcoholic fatty liver disease, obesity and the metabolic syndrome. *Best Practice & Research Clinical Gastroenterology.* 2014. Vol. 28, No. 4. P. 637-653.
DOI: https://doi.org/10.1016/j.bpg.2014.07.008

Licensed under CC BY 4.0

13. El-Kader S. M. A. Non-alcoholic fatty liver disease: The diagnosis and management. *World Journal of Hepatology.* 2015. Vol. 7, No. 6. P. 846-858. DOI: https://doi.org/10.4254/wjh.v7.i6.846

14. Filippova A. Non-alcoholic steatohepatitis in patients with obesity: interconnection between body mass, changes of lipid metabolism and concomitant pathology of biliary tract. *EUREKA: Health Sciences.* 2016. No. 4. P. 3-11. DOI: https://doi.org/10.21303/2504-5679.2016.00115

15. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention / Z. Younossi et al. *Nat Rev Gastroenterol Hepatol.* 2018. Vol. 15, No. 1. P. 11-20. DOI: https://doi.org/10.1038/nrgastro.2017.109

16. Liver fibrosis and hepatic stellate cells: Etiology, pathological hallmarks and therapeutic targets / C. Y. Zhang et al. *World J Gastroenterol.* 2016. 22. Vol. 48. P. 10512-10522.
DOI: https://doi.org/10.3748/wjg.v22.i48.10512

The article was received
2019.11.25