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解决非酒精性脂肪肝診斷難題的現代觀點
MODERN VIEW ON SOLVING DIFFICULTIES OF DIAGNOSING NON-ALCOHOLIC FATTY LIVER DISEASE

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抽象的。 目的一對現代診斷非酒精性脂肪肝患者前景的科學數據進行薈萃分析。 材料和方法。 對過去 10 年獲得的科學數據進行了分析，並使用「Web of Science、Scopus、eLibrary、RSCI 和 Google Scholar」進行分析。 結果。 科學資料的統合分析確定了 500 多項研究，其中僅選擇了 40 個來源作為研究對象。 結論。 因此，對科學數據的分析表明，儘管了解非酒精性脂肪肝的發病原因及其複雜性，但肝臟活檢仍然是評估肝臟健康的黃金標準。 在這方面，有必要引入易於使用的非影像工具和準確的生物標記物，借助它們不僅可以做出充分的診斷，而且可以在臨床試驗中有效評估 NAFLD 的新療法。

關鍵字：非酒精性脂肪肝（NAFLD）； 非酒精性脂肪肝的診斷。

Abstract. Objective *– meta-analysis of scientific data on prospects of modern diagnostics patients with non-alcoholic fatty liver disease.* ***Materials and methods.*** *Analysis of obtained scientific data was carried out over past 10 years and was carried out using «Web of Science, Scopus, eLibrary, RSCI and Google Scholar».* ***Results.*** *Meta-analysis of scientific data identified more than 500 studies, of which only 40 sources were selected as object of study.* ***Conclusion.*** *As a result, analysis of scientific data revealed that despite understanding of pathogenetic causes of non-alcoholic fatty liver disease and complexity of this disease, liver biopsy still remains gold standard for assessing liver health. In this regard, there is a need to introduce accessible non-imaging tools and accurate biomarkers, with help of which it will be possible not only to make an adequate diagnosis, but also, in clinical trials, to effectively evaluate new treatments for NAFLD.*

Keywords: *non-alcoholic fatty liver disease (NAFLD); diagnosis of non-alcoholic fatty liver disease.*

Introduction. Non-alcoholic fatty liver disease (NAFLD) is one of most common chronic liver diseases in industrialized countries, in regions such as Europe, Asia and United States [1]. Prevalence of liver pathology is rapidly progressing, with presence of NAFLD worldwide accounting for 25.0% of adult population. And ratio incidence of NAFLD among men and women is 1:1, with most common age among patients in this category being 45 years [2]. Clinically, NAFLD ranges from a fairly innocuous, benign condition to nonalcoholic fatty liver disease (NAFL) or nonalcoholic steatohepatitis (NASH). In addition, there is clinical evidence that NAFLD can progress to liver fibrosis and cirrhosis [3, 4]. Despite unfavorable risks of more severe or even life-threatening conditions during course of NAFLD, today there is no universal method of therapeutic intervention for NAFLD depending on stage of pathological process [5]. On the one hand, choice of drugs that are potentially effective for treatment of NAFLD remains controversial; on other hand, type of conservative therapy directly depends on stage and advanced stage of NAFLD [6]. As a rule, diagnosis of NAFLD is based on ultrasound examination of liver and biochemical indicators of liver enzymatic activity. However, there are increasingly more publications on use of ultrasound elastography of liver, radiological diagnostic methods and some forms of genetic testing, which largely encourages prospects for improvement in approaches to comprehensive medical care for patients suffering from NAFLD. This meta-analysis focuses on laboratory diagnostic options, including genetic tests and imaging techniques, used to diagnose different stages of NAFLD.

Objective is to evaluate status and capabilities of modern types of diagnostics of non-alcoholic fatty liver disease as part of a meta-analysis of scientific data.

Materials and methods. Design and structure of study was organized in accordance with international protocol for systematic reviews and meta-analyses “PRISMA-2009”. A search for scientific publications devoted to study of diagnosis of patients with NAFLD was carried out in «Web of Science, Scopus, eLibrary, RSCI and Google Scholar». Analysis of obtained data was carried out among scientific papers published between 2013 and 2023 (the error, in form of later studies, was used in isolated cases when it came to fundamental scientometric data). Study included 693 scientific articles; after an audit procedure for comparison of topics and absence of duplicates, 40 sources were included.

Results. In clinical practice, NAFLD is defined as fatty infiltration of liver accounting for more than 5.0% of liver weight, or presence of more than 5.0% of hepatocytes loaded with large fat vacuoles [7]. Basic condition for diagnosing NAFLD is absence of a cause of fatty liver disease such as alcohol and fact

that NAFLD has a heterogeneous development and many manifestations, including hepatocellular carcinoma [8]. When a diagnosis of NAFLD is suspected, it is important to exclude alternative causes of fat accumulation in liver or to rule out signs of liver dysfunction. At the moment, gold standard for diagnosing NAFLD is a liver biopsy, but its implementation carries a lot of inconvenience for both specialists and patients [9]. In general, a comprehensive clinical examination of patients with suspected NAFLD includes collection of a complete medical history, including exclusion of systematic alcohol consumption, certain groups of medications, family history and presence of viral liver diseases. Laboratory diagnostics basically include biochemical screening, serological testing of hepatitis B and C markers, determination of liver autoantibodies, immunoglobulins, concentration of α-1-antitrypsin, ferritin and ceruloplasmin in patients under 50 years of age. NAFLD is most often suspected clinically when a person with features of metabolic syndrome exhibits elevated serum aminotransferase levels, but nearly 80.0% of patients with NAFLD do not have biochemical abnormalities, which has several possible explanations. Thus, when analyzing ALT, experts often overestimate upper limit of normal, since calculation of hematological indicator is carried out without taking into account data from undiagnosed liver diseases, including NAFLD [10]. In the largest study, D.Prati et al. (2002), biochemical parameters of ALT were analyzed, subject to mandatory exclusion from study of persons at risk of liver dysfunction, obesity or diabetes. As a result, authors suggested that most sensitive ALT value for diagnosing NAFLD would be 30 U/L for men and 19 U/L for women. In addition, aminotransferase levels usually decrease significantly as NAFLD progresses and liver fibrosis develops. Consequently, in later stages of disease, biochemical indicators of liver function may be within normal limits [11].

Metabolic syndrome and its components are closely associated with occurrence of NAFLD. In almost two-thirds of obese people with T2DM, as well as in half of patients with hyperlipidemia and hypertension, liver ultrasound reveals fat deposition in parenchymal area [12]. To specifically identify NAFLD and its association with metabolic syndrome, diagnostic tools have been developed that have proven themselves in clinical practice. The most popular of these methods is index of steatosis or fatty degeneration of liver parenchyma (Fatty Liver Index - FLI). This diagnostic method includes, in addition to ultrasound, assessment of BMI, waist circumference, gamma-glutamyltransferase (GGT), and TG. Second diagnostic tool is Liver Fat Score (LFS). LFS score for NAFLD includes assessment of predictors such as metabolic syndrome, type 2 diabetes, fasting serum insulin, aspartate aminotransferase (AST) and ALT, as well as ratio of these enzymes. Both diagnostic algorithms are widely used in clinical practice and have a close correlation with more objective indicators of steatosis observed with ultrasound [13, 14].

At the moment, various methods of imaging liver are available, but abdominal ultrasound is the most pragmatic, radiation-free and relatively inexpensive

diagnostic method. Liver ultrasound is widely used and is a routine first-line diagnostic method [15]. Ultrasound has several significant advantages, which include non-invasiveness, lack of radiation exposure, accessibility and relative ease of use. In addition, ultrasound can be used to assess changes in parenchymal structure and identify various liver lesions. In cases with severe NAFLD or development of NSG, ultrasound has good sensitivity (85.0%) and specificity (95.0%). However, in initial forms of NAFLD, when number of steatotic hepatocytes varies from 20.0% to 30.0%, ultrasound is an ineffective diagnostic method [16]. Another problem with ultrasound diagnosis of NAFLD is liver fibrosis [17]. Since fibrosis phenomena can be cause of increased echogenicity of liver, which largely reduces ability to visualize fatty deposits [18]. More advanced techniques are being used to overcome limitations of ultrasound in assessing early manifestations of NAFLD. For example, Controlled Attenuation Parameter (CAP™), which uses vibration electrography to measure degree of ultrasound attenuation due to liver fat. V. eLedinghen et al. (2014) conducted a study in which they found that use of CAP could detect a milder degree of hepatic steatosis compared with conventional ultrasound. In addition, authors state that SAR correlates well with liver biopsy for diagnosing NAFLD [19]. Another innovation has been computer-assisted quantitative methods, such as combined liver echo intensity ratio followed by estimation of rate of decay of echo intensity. This method has a high level of sensitivity and specificity, and also allows you to detect steatosis if less than 15.0% of liver is affected. In recent years, a diagnostic method for NAFLD, such as computed tomography (CT), has become widely used. Like ultrasound, CT is easy to use and has relatively widespread use in clinical practice. Reliability of CT is due to its high specificity and sensitivity in diagnosis of NAFLD with moderate and severe steatosis. Unfortunately, this method is also unreliable when level of hepatic steatosis is low. In addition, potential hazard of ionizing radiation makes CT unsuitable for longitudinal follow-up of patients with NAFLD [20].

Most accurate and preferred method for diagnosing NAFLD is magnetic resonance imaging (MRI). MRI methods are very accurate in detecting hepatic steatosis, only limitation is examination modes. Thus, for diagnosis of NAFLD and visualization of steatosis, T1-weighted, T2 mode is used, which makes it possible to achieve interference of proton signal in adipose tissue [21]. With time and clinical experience with MRI, several methods have been developed with higher accuracy than classical MRI modes. One such method is MR spectroscopy (MRS), which measures fat fraction in liver with proton density. At the moment, MRS is not a publicly available method and is time-consuming [22, 23]. Another modernized method, Liver Multi Scan (LMS), uses traditional MRI technology but combines two or more quantitative methods to assess LIF liver inflammation and fibrosis. According to research by M. Pavlides et al. (2017), LMS with LIF assessment

demonstrated high diagnostic accuracy, even in comparison with morphological methods for diagnosing NAFLD. Unlike acoustic methods, LMS is not affected by central obesity, and this method can accurately visualize parts of liver involved in process of steatosis [24]. MR elastography (MRE), particularly 3D MRE imaging modality, has demonstrated superiority over ultrasound techniques for assessing fibrosis in NAFLD [25]. MRE has a significant drawback, which is that this diagnostic method is available only to specialized medical institutions in developed countries. This makes MRE practically unsuitable for widespread use.

Given understanding that NAFLD can develop among patients without clinical metabolic syndrome, introduction of genetic testing has recently become increasingly popular. In case of NAFLD, main attention is paid to identification of patatin-like phospholipase protein gene (PNPLA-3). Which is responsible for encoding membrane-binding function of hepatocytes and adipocytes. Main role of this protein structure is hydrolysis of TG in liver and concomitant excretion of low-density lipoproteins (LDL), [26]. According to SSLee et al. (2014), PNPLA-3 single nucleotide polymorphism “I-148M” (rs738409) is observed in approximately 20.0% of patients suffering from NAFLD. Also, presence of PNPLA-3 polymorphism indicates a violation of enzymatic activity of liver, hydrolysis of triglycerides and, as a consequence, a violation of LDL secretion [27, 28]. As a consequence, PNPLA-3 polymorphism indicates increased steatosis and inflammatory phenomena in liver [29]. There are a number of genes that have been reliably proven to be associated with NAFLD, including TM6SF2 gene (rs58542926), polymorphism of which reflects excessive secretion of oLDL . TMF6SF2 is a transmembrane gene and plays a critical role in enrichment of triglycerides to apoliprotein state. Thus, sequencing of this gene can be guaranteed to reflect a disorder in form of excess liver triglycerides and an inevitable decrease in level of circulating lipoproteins, which indicates disorders likely associated with NAFLD [30, 31]. LYPLAL1 gene, in rs12137855 variation, which has function of triglyceride catabolism, is however under study. Several variants (rs780094 and rs1260326) of GCKR gene polymorphism, reflecting degree of de novo regulation of lipogenesis. This genetic marker reflects level of glucose influx into hepatocytes, simultaneously controlling actions of glucokinase in liver. GCKR missense mutation encoding p446L protein is a marker of association of fat accumulation in liver and allows early differentiation of NAFLD [32]. LPIN1 gene and its variation rs13412852 reflect regulatory function of lipid metabolism. LPIN1 gene is a phosphatide phosphatase and regulates lipid metabolism by participating in synthesis of phospholipids and triglycerides, acting as an inducible transcriptional coactivator of fatty acid metabolism. These properties of LPIN1 make it possible to determine with high probability presence of NAFLD in patients [33, 34]. Variants of mitochondrial associated genes SOD2 (rs4880) and UCP2 (rs695366), responsi-

ble for function of mitochondrial antioxidant and mitochondrial lipid metabolism (OxPhos), allow us to determine a violation in mechanism of fatty acid oxidation. Violations of these functions can lead to a lack of protection of hepatocytes from free fatty acids, which in turn leads to accumulation of reactive oxidative elements and development of NAFLD. As well as variations (rs1044499 and rs1801278) for ENPP1 and IRS1 genes, respectively, which demonstrate an inhibitory response to insulin signaling pathway. Since polymorphism of these genes involved in interaction between insulin receptors in liver and direct transmission of signals from them, and signaling pathway itself is directly associated with fibrosis, sequencing data for ENPP1 and IRS1 are of particular importance in diagnosis of NAFLD as markers of insulin resistance and fibrosis [35].

Recently, a type of diagnosis such as epigenetics has become increasingly popular, due to emergence of data on gene expression and phenotypic variations that are not associated with changes in DNA chain sequence, but lead to NAFLD. One of these methods includes tests of non-invasive biomarkers, namely non-coding RNA (nc-RNA) test - F. Nassir et al. (2022), [36]. Need to develop non-invasive biomarkers is due to possibility of differentiating simple hepatic steatosis from NAFLD, NSG and early fibrosis. Most human RNA transcripts do not encode proteins; ncRNAs include short RNAs (<30 nucleotides) such as microRNAs (m-RNAs) and long non-coding RNAs (>200 nucleotides) such as circular RNAs (circular RNAs). [37, 38]. ncRNAs regulate cell physiology and function through epigenetic gene silencing and post-transcriptional regulation of mRNA stability. According to X.Qian et al. (2022) dysregulation of this process and abnormal expression of nc-RNA are directly associated with occurrence of NAFLD [39]. What is noteworthy is that in a recent study by Z. Fang et al. (2021), provide data and pay special attention to analysis of role of exosomal m-RNAs in NAFLD. Circulating m-RNAs, including m-RNA-122, m-RNA-34, m-RNA-192 and m-RNA-375, were increased in NAFLD and positively correlated with disease severity [40]. Specific for patients with NAFLD is a change in m-RNA-122 (more than 70.0% of total liver m-RNA pool). In large clinical studies, mRNA-122 levels were significantly increased in serum of patients with NAFLD and have been proposed as a potential biomarker for NAFLD and its progression [41, 42].

The most accurate method for diagnosing NAFLD and NSG still remains a liver tissue biopsy. Although biopsy is standard of care for diagnosing NAFLD, its use poses a clinical challenge in management of patients with NAFLD. Performing serial liver biopsies is expensive and completely unacceptable for both patients and healthcare professionals. Of course, liver biopsy should be considered in all cases that pose problems associated with risk of developing liver malignancies. Additionally, in individuals with a high likelihood of liver fibrosis, a biopsy may be used to confirm diagnosis.

Conclusions. NAFLD is a highly common disease that is prevalent in most countries of the world. Pathogenesis of NAFLD is associated with insulin resistance and hyperlipidemia, which lead to development of damage not only to liver, but also to other organs and systems. In particular, blood vessels, heart and pancreas, thus exacerbating life prognosis of this group of patients. Thereby emphasizing characteristics of patients, importance of diagnosis and complexity of choosing therapeutic tactics for treatment of NAFLD. Often low sensitivity of standard diagnostic methods does not lead to an adequate diagnosis, and this is due to multifactorial nature of causes of NAFLD, as well as complete lack of accessible and inexpensive imaging tools and lack of adequate non-invasive biomarkers. This literature review summarized modern types of diagnostic mechanisms, including epigenetics, as a potentially effective option for diagnostic screening of NAFLD.

Conclusion. Despite these limitations and high risk of sampling error, liver biopsy remains standard of care for evaluation of NAFLD. In this regard, there is a need to introduce accessible non-imaging tools and accurate biomarkers, with help of which it will be possible not only to make an adequate diagnosis, but also, within framework of clinical trials, to analyze effectiveness of modern methods of treating NAFLD.

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