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NON-ALCOHOLIC FATTY LIVER DISEASE – A RAPIDLY GROWING INDICATION FOR LIVER TRANSPLANTATION IN THE MODERN WORLD

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Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in many countries, involving about 25% of the population worldwide. This disease includes many genetic, metabolic, and environmental factors. It is closely associated with insulin resistance, metabolic syndrome, obesity, diabetes, and many other diseases. NAFLD is characterized by macrovesicular steatosis of the liver. In the natural course of NAFLD simple steatosis progresses to nonalcoholic steatohepatitis (NASH), fibrosis and ultimately, cirrhosis and hepatocellular carcinoma. Cirrhosis with Nash and hepatocellular carcinoma is an indication for liver transplantation. Obesity is a growing problem in liver transplant candidates. Cardiovascular complications related to metabolic syndrome and NASH recurrence in the transplanted liver may affect the outcome of surgery in these patients. The results after transplantation are similar to the results of liver transplantation for other indications, but cardiovascular complications are the main cause of death in patients with NASH after surgery.

Keywords: nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, liver transplantation.

INTRODUCTION

The initial description of non-alcoholic fatty liver disease (NAFLD) dates back to 1980 and belongs to J. Ludwig et al. [1]. NAFLD is defined as an abnormal accumulation of fat in the liver in the absence of other chronic liver diseases, for example, hepatitis C, or secondary steatosis with drug addiction, alcoholism, hereditary metabolic disorders, etc. Due to the ongoing persistence of obesity, NAFLD has become the most common cause of chronic liver disease worldwide, including in developing countries [2, 3]. In developing countries, up to one-fifth of the population suffer from NAFLD, and in developed countries, prevalence reaches 35% [4].

This problem became most severe first in USA and Western Europe. In Russia, NAFLD is also becoming an increasingly common disease, which has been drawing the attention of Russian researchers. Several research papers on this subject have been published in recent years [5–9]. The study of the clinical and laboratory-instrumental features of liver and biliary tract function, as well as the effectiveness of combination therapy in NAFLD, were the focus of a major study by E.V. Suchkova [10]. Clinical and metabolic features of non-alcoholic fatty liver disease in children are described in the work of E.N. Kutyreva et al. [11]. Based on epidemiological studies in Russia in 2015 under the editorship of Professor V.T. Ivashkina from the Russian Academy of Sciences, guidelines for doctors on diagnosis and treatment of non-alcoholic fatty liver disease were published [12].

In the natural course of NAFLD, the disease progresses, and simple fatty liver transforms into non-alcoholic steatohepatitis (NASH) with the development of fibrosis, which progresses to cirrhosis [13]. NAFLD is the main cause of hepatocellular carcinoma, while other chronic diseases lead much less frequently to liver cancer [14, 15].

With the development of NASH-related cirrhosis, and even more so with hepatocellular carcinoma, liver transplantation is a non-alternative treatment method [2, 4, 16–18].

EPIDEMIOLOGY OF NAFLD

Non-alcoholic fatty liver disease is highly prevalent on all continents. The prevalence of NAFLD in South America is 31%, in the Middle East – 32%, in Asia – 27%, in USA – 25.8% and in Europe – 23%. The global NAFLD prevalence is in the range of 22–29%, with an average of 25% [19]. NASH prevalence is estimated to be in the range of 1.5% to 6% [20, 21]. However, among patients whose diagnosis was based on the results obtained from liver biopsy, NASH was detected in 59.1% of cases [19].

Two major epidemiological studies of NAFLD were carried out in Russia. In the first of them (DIREG 1, 2007), it was found that the average NAFLD prevalence

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in 30,754 outpatients examined was 27%; the southern regions of the European part of Russia had the lowest prevalence (19.6%), while Siberia accounted for the highest (31.6%) [22–24].

The world's largest study, the second Russian epidemiological study (DIREG 2, 2013–2014) on NAFLD prevalence was conducted in 16 cities across Russia. It featured over 50,000 outpatients. According to the DIREG 2 study, NAFLD prevalence significantly increased by 10% to reach 37.3% against the first DIREG 1 study [24, 25]. L.K. Palgovoy et al. [24] presented the results of a study on NAFLD prevalence in the Northwest region of Russia. The incidence of NAFLD in this region was much higher than the national average: Of the 3,769 patients examined in this region, NAFLD was diagnosed in 49.1% of them.

In Mexico, a retrospective multicenter study of the etiology of cirrhosis was conducted from January 2012 to December 2017. A total of 1,210 patients were examined. The most common causes of cirrhosis were hepatitis C virus (36.2%), alcoholic liver disease (31.2%) and NASH (23.2%). The least common were hepatitis B virus (1.1%), autoimmune disorders (7.3%) and other conditions (1.0%). It was noted that in recent years, NAFLD, as an etiology of cirrhosis, increased by 100% and will soon become one of the most frequent etiological causes of cirrhosis in Mexico [26].

NAFLD was reported in Japan almost 50 years ago in genetically susceptible people with irrational (excess) nutrition. People in Asian countries are especially susceptible to NAFLD. Prevalence ranges between 20% (China), 27% (Hong Kong) and 15–45% (South Asia, Southeast Asia, Korea, Japan, and Taiwan) [27].

A recent study [28] presented a very disappointing picture obtained by predicting the progression of NAFLD prevalence in the United States until 2030. It was forecasted that prevalent NAFLD cases would increase by 21% – from 83.1 million in 2015 to 100.9 million in 2030 and NASH prevalence would increase by 63% from 16.52 million to 27.00 million. In 2030, the overall prevalence of NAFLD among the adult population aged 15 years and above is projected at 33.5% in 2030. Between 2015 and 2030, prevalent NAFLD cases among the median age will increase from 50 to 55 years. In 2015, approximately 20% of the total number of NAFLD patients suffered from NASH, and their number is projected to increase to 27% by 2030. By 2030, incidence of decompensated cirrhosis will rise by 168% to 105,430 patients, while incidence of hepatocellular carcinoma will rise by 137% to 12,240 patients. Mortality from NAFLD is expected to increase 178% to about 78,300 deaths in 2030 [28].

NAFLD is found not only in adults but also in obese children [11, 29]. The study by E.N. Kutyreva et al. [11] included 869 obese and overweight children between the ages of 3 to 17 years – an average of 12.2 ± 0.2 years. NAFLD was diagnosed in 335 (39%) patients. Based on clinical and laboratory examination, all the children were divided into two groups: Group 1 – non-alcoholic fatty liver (NAFL) (n = 228), Group 2 – NASH (n = 107). The prevalence of NASH increased side-by-side with an increase in the length of obesity and its degree.

NAFLD distribution by gender varies by age: the lowest male/female ratio (0.94) is observed among people under 30 years old, and the highest (1.31) among people aged 40–49 years [28]. The Third National Health and Nutrition Examination Survey in the United States (NHANES-III), which included 3271 people aged 60 years and above, found that NAFLD was prevalent in the elderly. NAFLD is associated with higher risk of mortality for people aged 60–74 years but was lower in those older than 74 years [30]. NAFLD prevalence is also affected by ethnic differences. In the USA, the highest rate of NAFLD is seen among Hispanics (45%), followed by whites (33%) and even lower among African Americans (24%) [31].

In different regions of the world, both similarities and differences in the epidemiology of NAFLD have been noted. For example, the condition is associated with obesity and insulin resistance in most individuals in Western countries, while the disease manifests at a lower body mass index in Asia, and many patients seem to lack insulin resistance [32].

PATHOGENESIS OF NAFLD

NAFLD is a complex and multisystem disease that has a high socio-economic impact [33]. It is believed that the pathogenesis of NAFLD is based on metabolic syndrome, insulin resistance and hyperinsulinemia [34]. These conditions are associated with the obesity epidemic in many countries of the world, especially in the United States [7, 9, 19, 35]. Most NAFLD patients are overweight (body mass index of 26.3–34.0 kg/m^2, a median of 29.4 kg/m^2) [36].

Insulin resistance is increasingly recognized as a key factor linking metabolic syndrome and NAFLD. Insulin resistance leads to insufficient inhibition of hepatic gluconeogenesis, increased lipid accumulation, and decreased glycogen synthesis [37]. Circulation of inflammation-enhancing free fatty acids is increased, overexpression of proinflammatory cytokines occurs and Kupffer cells are activated, which also promotes insulin resistance. Endoplasmic reticulum stress and inflammation, in turn, exacerbate and maintain the insulin-resistant state, forming a vicious circle [38].

An increase in the total cholesterol to high-density lipoprotein cholesterol ratio is a predictor of both cardiovascular disease and NAFLD [39]. Since in addition to insulin resistance, NAFLD signs include hypertriglyceridemia, a mandatory study of not only carbohydrate but also lipid metabolic processes in patients with liver

steatosis is necessary for the timely correction of disorders in order to reduce progression of this disease [7, 9].

Metabolic syndrome occurs with various risk factors, such as obesity, type 2 diabetes or dyslipidemia. The prevalence of this syndrome is increasing worldwide along with an increase in obesity, and there is evidence to suggest a link between NAFLD and metabolic syndrome [34, 40]. NAFLD is also considered the "hepatic manifestation" of metabolic syndrome [34]. It is important to note that most patients with NAFLD have at least one risk factor for metabolic syndrome [38].

Numerous clinical data have confirmed the existence of a bi-directional relationship between NAFLD and various components of the metabolic syndrome, especially type 2 diabetes [34, 41, 42]. A recent study [36] has shown that almost 50% of NAFLD patients suffer from diabetes. It should be borne in mind that NASH is only one of the risk factors for developing diabetes after liver transplantation. This complication is a multicausal pathology. The main reason for developing post-transplant diabetes is the use of calcineurin inhibitors as immunosuppressive agents. Pretransplant obesity and HCV infection are additional risk factors. Post-liver transplantation diabetes mellitus develops in up to 30% of liver transplant recipients [43].

Clinical evidence also suggests that NAFLD may contribute to the development of cardiovascular disease [14]. The risk of developing hypertension and atherosclerosis is parallel to NAFLD severity. A close relationship was found between NAFLD and mortality from these diseases [14, 44, 45].

Based on a study of a database of patients requiring liver transplantation (n = 138,021), type 2 diabetes, obesity, age 60 and above, female gender, and white race were found to be the strongest predictors of NASH. Type 2 diabetes was more common in patients with NASH (53%) than in patients with cryptogenic cirrhosis (29%), alcoholic cirrhosis (16%) and autoimmune hepatitis (16%). Obesity was more common in patients with NASH (65.3%) than in the other three groups (33–42%). The NASH patient group had more white people (82.3%) and fewer black, Hispanic and Asian people than in the other three groups. Hepatocellular carcinoma was more often observed with NASH (19% *vs*. 9–13% in other groups). Incidence of tumor development did not depend on obesity and type 2 diabetes [46].

NASH compared with non-alcoholic fatty liver (NAFL) is significantly more often accompanied by dyslipidemia (72%), hyperinsulinemia (37%), formation of metabolic syndrome (39%) and a low rate of fat oxidation (58.01 ± 8.02 g/day and 78.55 ± 4.85 g/day, respectively) [11].

In recent years, it has been shown that there is genetic predisposition in NAFLD [14, 29, 31, 47, 48]. Obesity enhances the genetic risk of NAFLD, which is associated with the PPNPLA3 p.I148M, TM6SF2 p.E167K and GCKR p.P446L polymorphisms [49, 50]. In an East European population, it was shown that PNPLA3 and RNF7 gene variants are associated with the risk of developing liver fibrosis and cirrhosis [51].

Genetic studies have revealed some genetic modifiers that influence the severity and progression of the disease, for example, the PNPLA3 (patatin-like phospholipase domain-containing protein 3) gene variant [48]. It was also found that epigenetics, particularly DNA methylation, increases insulin resistance and NAFLD severity [52].

Association of IL6R gene polymorphic variant rs2228145(C>A) with the development of NASH in Karelia residents has been found. The risk of developing NASH is more than 2-fold higher in carriers of CC genotype by rs2228145 polymorphic marker than in carriers of other genotypes. Plasma IL-6 levels and the content of IL6R gene transcripts in the peripheral blood leukocytes are higher in NASH patients than in healthy people. Gene IL6R polymorphic variant rs2228145(C>A) is probably involved in genetic predisposition of the Karelian population to NASH [53].

Thus, the main independent predictors of NAFLD and, by inference, potential targets for treatment are metabolic syndrome, insulin resistance, increased serum uric acid, alanine aminotransferase and serum total cholesterol [54]. Insulin resistance related to metabolic syndrome, being the main pathogenetic trigger that, combined with adverse genetic, humoral, hormonal, and lifestyle factors, accelerates development of NAFLD [14].

The pandemic of obesity and its associated complications are rapidly changing the epidemiology of many types of cancers, including hepatocellular carcinoma. NAFLD is becoming a major cause of development of hepatocellular carcinoma, with a steadily growing trend compared to viral or alcohol-induced chronic hepatitis. The higher prevalence of NAFLD in the general population and the likelihood of hepatocellular carcinoma occurring in a non-cirrhotic liver are the most disturbing aspects. Currently, systemic and hepatic molecular mechanisms involved in hepatocarcinogenesis, as well as potential early markers of hepatocellular carcinoma, are being comprehensively studied [15].

DIAGNOSIS OF NAFLD

Considering the dramatic increase in NAFLD prevalence, the urgent need to develop non-invasive, simple, reproducible and reliable methods for diagnosing this disease has long been talked about. Such methods can be useful not only in NASH diagnosis but also in evaluating response to treatment and further prognosis [14, 36]. Non-invasive serum biomarkers are a simple means of sequential observation [55]. To diagnose the progression of post-liver transplant NAFLD-related fibrosis, numerous non-invasive methods have been developed, which are described in detail in the work of Z. Galvin et

al. [36]. However, to date, despite numerous limitations, liver biopsy is the most accurate method for diagnosing fibrosis.

The final correlation when using any new test is carried out by comparing with the results of a study of liver biopsy samples. Histological analysis of liver biopsies remains the "gold standard" test against which other methods of assessment for the presence and amount of hepatic injury due to NAFLD are measured. Histological evaluation remains the sole method of distinguishing liver steatosis from advanced forms of NAFLD, i. e. NASH, assessing the degree of fibrosis and diagnosing hepatocellular carcinoma [14, 56]. Liver biopsy is both confirmation of the diagnosis and evaluation and semiquantitation of injury to the parenchyma, fibrosis, and evaluation of architectural remodeling of the liver [56].

However, liver biopsy suffers from challenges. First is that the procedure is invasive. Secondly, a small amount of biopsy. An adequate biopsy represents only 1/50,000–1/65,000 of this large organ. Therefore, puncture needles of a suitable size and sampled area should be carefully chosen. Thirdly, there may be morphological differences between the right and left lobes of the liver. Fourthly, the length of the biopsy is critical. With a ≥1.5 cm length, diagnosis is much more accurate than with a <1 cm length. Finally, experienced pathologist is important to correctly interpret liver biopsy results [56].

PATHOMORPHOLOGY OF A LIVER WITH NAFLD

In NAFLD, a wide range of histological changes occurs, ranging from non-alcoholic hepatic steatosis to severe NASH [57]. About a quarter of patients with NAFLD develop NASH [3]. Therefore, morphological changes in a liver with NAFLD depend on the stage of the disease. According to the latest definition by the American Association for the Study of Liver Diseases (AASLD), two components are necessary for diagnosis of NAFLD: 1) evidence of hepatic steatosis either by imaging or histology; and 2) lack of secondary etiologies of hepatic steatosis, including significant alcohol consumption, adverse drug effects and/or hereditary disorders [57].

Histologically, NAFLD is subdivided into NAFL and NASH.

Non-alcoholic fatty liver (NAFL). At the NAFL phase, fatty degeneration of hepatocytes takes place with accumulation of triglycerides in their cytoplasm. The presence of more than 5% of hepatocytes with macrovesicular steatosis is the minimum criterion for histological diagnosis of NAFL. Fatty liver is divided into three by severity: I (mild) – above 5% and up to 33% of hepatocyte steatosis; II (moderate) – above 33% and up to 66%; III (severe) – above 66%. Steatosis is usually macrovesicular, but may be mixed (a combination of macrovesicular with microvesicular hepatocyte obesity). An intracytoplasmic large fat droplet or a few small drops displace the core to the periphery of the hepatocyte. A distinctive feature of steatosis in adults, unlike in children, is that steatosis initially affects hepatocytes in acinar zone 3 (perivenular). As the disease progresses, it spreads to the entire acinus [56]. With NAFL, foci of lobular and/or portal inflammation and lipogranulomas may be seen. Lobular inflammation is usually mild, consisting of a mixed inflammatory infiltrate, composed of lymphocytes, a small amount of eosinophils, and, sometimes, a few neutrophils. Foci of chronic lobular inflammation, consisting mainly of lymphocytes, are rarely seen. However, lobular and portal inflammation in NAFL are very rare, and their presence indicates the progression of the disease to NASH [58]. Slight siderosis might occur in periportal hepatocytes and/or pan-acinar reticulo-endothelial cells [56].

Non-alcoholic steatohepatitis (NASH). The minimum criteria for making histological diagnosis of NASH in adult patients, in addition to steatosis, include hepatocellular injury (usually in the form of ballooning degeneration) and lobular inflammation, typically localized in acinar zone 3 [31]. With ballooning degeneration, ballooned hepatocytes are enlarged, with swollen, rarefied, pale cytoplasm and, usually, show a large, hyperchromatic nucleus. Loss of hepatocyte keratins, 8 and 18, as detected by immunostaining, might help in the objective identification of ballooned hepatocytes, in the presence of which more aggressive course of the disease and high incidence of cirrhosis and metabolic syndrome are noted. Increased hepatocyte apoptosis, as well as hepatocyte necrosis, are also morphological signs of NASH. In NASH, hepatocytes can have giant round or needle-shaped mitochondria. Giant mitochondria are more commonly observed in hepatocytes with microvesicular steatosis. Electron microscopic examination shows that in these mitochondria, there is loss of cristae, membranes and paracrystallin inclusions. NASH is characterized by the presence of large vacuolated nuclei usually observed in periportal hepatocytes. Liver biopsy specimens contain lobular microgranulomas (Kupffer cell aggregates) and lipogranulomas [56].

Fibrosis is not a necessary diagnostic feature of NASH. Nevertheless, based on a meta-analysis of the results of a punctate study of paired liver biopsies specimens performed at least 1 year apart, liver fibrosis progresses in patients with NASH [59]. Fibrosis typically begins in acinar zone 3 and has a fine mesh pattern, since collagen and other components of the extracellular matrix of connective tissue grow perisinusoidally and around hepatocytes. Perisinusoidal fibrosis in NASH, as in other chronic liver diseases, is probably the result of Kupffer cell activation. In hepatocytes in acinar zone 3, there may be eosinophilic intracytoplasmic inclusions located close to the nucleus (Mallory bodies). Portal fibrosis usually occurs after appearance of perisinusoidal and pericellular fibrosis. More severe fibrosis (F2–F4)

develops later. Cirrhosis (F4) in NASH is macronodular or mixed. Steatosis may not persist with the progression of fibrosis, especially in cirrhosis, as well as in architectural remodeling of the liver [56]. Progression of the disease to cirrhosis can lead to hepatocellular carcinoma and liver failure [31].

Histologically, NASH is often indistinguishable from liver disease caused by alcohol use. Therefore, in diagnosis of NASH, a thorough clinical and anatomical analysis is required to exclude the alcoholic nature of the disease. Unfortunately, in most patients with NASH, cirrhosis is diagnosed by chance. Although its timely diagnosis is of great clinical importance, since cirrhosis has a high probability of developing other liver diseases, including hepatocellular carcinoma [60].

TREATMENT OF NAFLD

Radical lifestyle changes aiming at normalizing body weight is the basic therapeutic intervention to manage this disease. Insulin sensitizers, antioxidants, lipid lowering drugs, incretin-based drugs, weight loss medications and bariatric surgery may be necessary for management in some cases along with lifestyle measures [61]. G.C. Farrell et al. [27] believes that public health efforts to limit excess nutrition and reduce insulin resistance are necessary to prevent and/or reduce the development of NAFLD and its adverse health effects, such as type 2 diabetes, cardiovascular disease, cirrhosis and liver cancer. Comprehensive treatment of NAFLD patients, including the use of drug therapy, balneopeloid therapy and internal intake of mineral water, provides significantly faster relief of clinical manifestations of the disease and restores the motor activity of the gallbladder, compared to drug therapy alone [62]. Conservative and surgical treatment of NAFLD is described in detail in the Guidelines for physicians published by the Russian Society for the Study of the Liver [12]. In the terminal stage of the disease, orthotopic liver transplantation is the non-alternative treatment option [14].

LIVER TRANSPLANTATION FOR NASH-RELATED CIRRHOSIS

Although in most patients, the course of NAFLD is benign, in some patients, NASH develops with subsequent cirrhosis and the risk of developing decompensation and/or hepatocellular carcinoma. Both conditions are indications for orthotopic liver transplantation [63]. Due to increased incidence of metabolic syndrome and its components, NASH-related cirrhosis and NASH-related hepatocellular carcinoma will soon become the leading indication for liver transplantation in USA and in many other countries of the world [2, 64–68]. In addition, due to increase in the incidence of NAFLD, there are more steatotic donor livers and fewer "normal" organs for transplantation [2]. Despite the increase in the number of available donor organs, waitlist mortality remains a serious concern [66].

Recently, the International Liver Transplantation Consensus Statement on End-stage Liver Disease Due to NASH have been published. The purpose of these guidelines is to highlight specific features commonly observed in NASH patients and to present strategies to optimize the evaluation of pretransplant patients and waitlist survival [63].

Patients who have NASH and are candidates for liver transplantation are usually burdened with various comorbidities [33], such as obesity, type 2 diabetes, cardiovascular disease and kidney disease [2, 63, 64]. Compared with other liver transplant recipients, recipients with NASH are more likely to have diabetes mellitus (73.5% *vs*. 20%, $P < 0.01$), metabolic syndrome (83.3% *vs*. 37.8%, $P < 0.01$), cardiovascular diseases (29.4% *vs*. 11.1%, $P < 0.01$), urogenital infections ($P = 0.03$) [67]. Comorbidities directly affect evaluation and selection of patients, waitlist morbidity and mortality, and, ultimately, posttransplant outcomes [63]. In addition, recipients with NASH are at increased risk for pre-transplant portal venous thrombosis with decompensation of the native liver [69].

Compared with other recipients, recipients with NASH are older [18]: 58.5 ± 8.0 *vs*. 53.0 ± 8.9 years; $P < 0.001$ [70]; 59.2 *vs*. 54.8 years, $P = 0.01$ [69]. They often have a high body mass index [18]: 63% *vs*. 32%; $P < 0.001$ [70]; 61.8% *vs*. 8.1%, $P < 0.01$ [67] and higher MELD [18]. Among them there are more women (47% *vs*. 29%; $P < 0.001$) and they are more likely to have hepatocellular carcinoma (12% *vs*. 19%; $P < 0.001$) [70].

The most acute liver transplant problem in end-stage NASH and hepatocellular carcinoma is in the United States. Numerous recent studies have shown that NASH-related cirrhosis is rapidly becoming the leading indication for liver transplantation in the US [17, 71, 72]. After the start of the use of safe and effective direct-acting antiviral drugs in 2015, the need for liver transplantation in hepatitis C patients decreased. Therefore, according to current trends, it is suggested that in the US, NASH will overtake hepatitis C as the most common indication for liver transplantation over the next 10 years [4].

The trend towards an increase in the number of patients who underwent liver transplantation for NASH-related cirrhosis is clearly evident from several publications listed below. In the United States, 53,738 liver transplants were performed between January 1, 1997 and October 31, 2010. Towards the end of this period, NASH became the fourth most common indication for liver transplantation. The proportion of liver transplants performed for NASH-related cirrhosis increased dramatically from 1.2% in 1997–2003 to 7.4% in 2010 [73].

Another study showed that the number of patients with NASH-related cirrhosis increased from 1.2% in 2001 to 9.7% in 2009. At that time, NASH was the third

most common indication for liver transplantation in the United States [70].

Between 2004 and 2013, in the liver transplant waitlist in the United States, the number of patients with NASH increased by 170% (from 804 to 2174), with alcoholic liver disease – by 45% (from 1400 to 2024), and with HCV – by 14% (from 2887 to 3291), whereas the number of patients with HCV infection in combination with alcoholic liver disease decreased by 9% (from 880 to 803). In 2013, NASH became the second leading etiology of liver disease after HCV among patients awaiting liver transplantation in the United States [74].

To evaluate the incidence of liver transplantation associated with NASH, a retrospective cohort study utilizing the UNOS/OPTN database for 2003–2014 was conducted [75]. Overall, 63,061 adult patients, including 8262 (13.11%) NASH patients, underwent liver transplantation during this period. The incidence of NASH surpassed alcoholic liver disease, and since 2008, has become the second leading indication for liver transplantation. In 2014, 17.38% of all liver transplants were performed due to NASH. From 2003 to 2014, the number of liver retransplantations with NASH increased by 162%, with HCV – by 33%, and with alcoholic liver disease – by 55%.

In 2016, a total of 7841 liver transplants were performed in the United States. The average waiting time for an operation is 11.3 months [66]. The number of patients on the liver transplant waiting list and the number of liver transplants for HCV decreased, but the number of patients with NAFLD increased [17].

Improvement in the diagnosis of native liver diseases has shown that patients suffering from NASH cirrhosis often "hide" under the flag of cryptogenic cirrhosis. Therefore, the number of patients diagnosed with NASH in the United States from 2002 to 2016 increased from about 1% to 16%, while cryptogenic cirrhosis decreased from 8% to 4% [76].

NASH is thought to be a rare indicator for liver transplantation in young people. However, recently published studies [72] have shown that this view is wrong. A total of 5157 young adults (54% were men, 23% obese) underwent liver transplantation and the outcomes were analyzed. The median age and body mass index were 31.6 ± 6.7 years and 26.3 ± 6.1 kg/m, respectively. The incidence of liver transplantation performed for NASH-related cirrhosis increased from 0.53% in 2002 to 4.46% in 2012. NASH was the most rapidly growing indication for liver transplantation among all other etiologies with a 14% increment per year ($P < 0.001$). The 5-year post-liver transplantation survival were comparable between NASH and non-NASH recipients. However, transplant survival was lower (63.5% *vs*. 81.4%, $P = 0.003$), and retransplantation cumulative rates were higher in NASH recipients compared with those with other metabolic liver diseases (12.7% *vs*. 4.2%, $P = 0.046$). Thus, NASH is the fastest-growing indication for liver transplantation among young adults in the US aged 18 to 40 years, and currently accounts for almost 5% of all liver transplants in this age group.

In Nordic countries, NASH is also a growing indication for liver transplantation. Of the 4,609 patients listed for liver transplantation, the number of patients with NASH increased from 2.0% in 1994–1995 to 6.2% in 2011–2015 ($P = 0.01$) and became the second fastest-growing indication [18].

The global upward trend in obesity and diabetes has made NASH one of the leading indications for orthotopic liver transplantation in Australia and New Zealand [4]. This study showed that from 1994 to 2017, of 5016 patients listed for liver transplantation, the percentage of patients with NASH increased significantly ($P < 0.001$): from 2.0% in 2003 to 10.9% in 2017. In 2017, NASH was the third leading cause of chronic liver disease among wait-list registrants behind hepatitis C virus (29.5%) and alcoholic fatty liver disease (16.1%). Similarly, there was significant increase in the percentage of patients with NASH undergoing liver transplantation [4].

POSTTRANSPLANT RECURRENCE OF NASH

Development of liver graft steatosis is a significant problem after surgery, which may happen as a recurrence of pre-existing disease or de novo NAFLD [2, 33]. Recurrent NASH following liver transplantation occurs in connection with the continuation of the action of NAFLD risk factors. Additionally, immunosuppressive therapy has influence on metabolic balance, triggering insulin resistance, diabetes mellitus, hypertension, hyperlipidemia and obesity. No statistically significant difference in steroid dosage, cholesterol and triglyceride levels and body mass index was found in patients with recurrent NASH compared with patients without a recurrence [77]. Nevertheless, many patients develop posttransplant metabolic syndrome. Considering that NAFLD is a manifestation of metabolic syndrome, it is not surprising that both recurrent and *de novo* NAFLD occur after liver transplantation [78]. Posttransplant recurrence of NASH was more likely to occur in patients who had metabolic syndrome, hypertension, or insulin-dependent diabetes mellitus [77].

Patients with recurrent NAFLD have a higher risk of cardiovascular disease and kidney dysfunction [33], which may affect the outcome of liver transplants in these patients [78].

The first study on NASH recurrence rate after liver transplantation is from W.R. Kim et al. [79]. NASH was diagnosed based on histological examination of a removed native liver. Patients with significant alcohol consumption were excluded from the study. Of 622 liver explants, 8 patients had features consistent with NASH. All patients were female with a median age of 58. Fifteen months following liver transplantation, six

patients developed persistent fatty infiltration in their graft. In two patients, transition from mild steatosis to steatohepatitis and early fibrosis was observed over one to two years. The authors concluded that patients who underwent liver transplantation for NASH may develop recurrent steatosis shortly after transplantation, with possible progression to NASH and fibrosis.

Later, a report was published about recurrence of NASH in a 58-year-old woman who drank no alcohol and who underwent a liver transplant in mid-1993. After the operation, she suffered acute rejection crisis, which was successfully stopped, and by the ninth week after surgery, liver function tests returned to normal. However, at the 66th week after surgery, with persistent moderate increase in the level of alkaline phosphatase and gamma-glutamyl transferase, transplant biopsy unexpectedly revealed NASH recurrence. A second biopsy (76 weeks after liver transplantation) revealed NASH-related cirrhosis. A third biopsy at week 87 confirmed cirrhosis. The patient did not drink alcohol. Multi-targeted polymerase chain reaction was negative for HCV [80].

In a retrospective single-center study of 46 patients with NASH and 37 patients with cryptogenic cirrhosis who underwent liver transplantation between 1996 and 2008, 20 patients showed recurrent NASH, on average, 45.7 months after surgery [77].

In one of the latest studies comprising 56 patients, on average, 75 months after a liver transplant, ultrasound elastography measurements consistent with no fibrosis (42.9%) or F1–F2 fibrosis (30.4%), advanced fibrosis (F3) was noted in 26.8%, whereas F4 (clinically compensated) was 5.4% of patients. Thirty-four patients had liver biopsy on average 47 months after liver transplantation: 41.2% were diagnosed with recurrent NASH, bridging fibrosis was noted in 20.6% of patients, but no patients had cirrhosis [65].

Bhagat et al. [77] reported recurrent NASH in 33% of patients six months following liver transplantation. Recurrence of NAFLD five years following liver transplantation, according to literature sources, occurs in a wide range from 10.0% to 100.0%, and NASH from 4.0% to 28.0%. respectively [36].

DE NOVO POSTTRANSPLANT NAFLD

De novo posttransplant NAFLD is one of the serious conditions for patients suffering from various liver diseases [2, 33]. Z. Galvin et al. [36] identifies five predictors of *de novo* NAFLD development: weight gain, high body mass index, HCV infection, and sirulimus therapy. In the absence of these factors, *de novo* NAFLD develops in only 5.4% of patients, and in the presence of all five factors, NAFLD occurs in 100% of patients. All of these factors are associated with insulin resistance, and this may be the main reason for development of *de novo* NAFLD.

On average, three years after liver transplantation, one third of biopsy specimens showed histological signs of *de novo* NAFLD [36]. The authors emphasize that these were not protocol biopsies, therefore, based on biopsy data, it is impossible to determine the actual incidence of *de novo* NAFLD. About half of the patients had simple steatosis (48.2%), and the other half had NASH (51.8%). The incidence of *de novo* NASH in this study was significantly higher than that found by other researchers. The authors attribute this to the fact that patients were older at the time of liver transplantation, among them there were more diabetic patients and patients with a higher body mass index. Histological evaluation of liver transplant biopsy samples showed significant fibrosis (F2–3) in almost 40.0% of patients with *de novo* NAFLD, and cirrhosis (F4) in more than 5.0% of patients. Moreover, the rate of transplanted liver fibrosis in *de novo* NAFLD in patients suffering from HCV or autoimmune diseases is higher than in the native liver of recipients suffering from NAFLD.

There are several reasons for accelerated progression of posttransplant fibrosis: rapid weight gain after surgery, resumption of metabolic syndrome and adverse effects associated with immunosuppressive therapy such as arterial hypertension, dyslipidemia, insulin resistance and diabetes mellitus [3]. Development of the main one – *de novo* metabolic syndrome is facilitated by high steroid dosage after liver transplantation (5.2 ± 2.4 mg/day *vs*. 7.1 ± 4.7 mg/day, P = 0.014) [81]. Within two years following liver transplantation, *de novo* metabolic syndrome affected 32.9% of 170 patients. Multivariate analysis identified glycosylated hemoglobin levels equal to or higher than 5% (P = 0.003), diabetes mellitus (P = 0.002), and arterial hypertension (P = 0.009) as independent risk factors for developing *de novo* metabolic syndrome. Incidence of metabolic syndrome correlates with high steroid dosage (5.2 ± 2.4 mg/day *vs*. 7.1 ± 4.7 mg/day, P = 0.014), with NAFLD (P = 0.001) and dyslipidemia (P = 0.013) [81].

Posttransplant graft steatosis of a part of the liver from living donors was detected in biopsy specimens in 33 patients, with NASH diagnosed in 9 of the 33 patients. Recipients with liver steatosis were younger than those without steatosis (53.4 ± 9.5 years *vs* 57.6 ± 9.9 years, respectively; P = 0.045). It should be noted that prevalence of steatosis was significantly higher among recipients who received a graft from a donor with steatosis than without (60% *vs* 23%, respectively; P = 0.001). On multivariate analysis, younger recipient age (P = 0.023) and donor steatosis (P = 0.005) were independent risk factors of liver steatosis after liver transplantation. The clinical course of steatosis is relatively benign, with only 19% developing NAFLD, and 7.6% developing severe fibrosis [82].

LIVER TRANSPLANTATION OUTCOMES FOR NAFLD

Non-alcoholic fatty liver disease increases patients' morbidity and mortality [14]. The presence of morbid obesity (BMI ≥ 40 kg/m^2) and diabetes are independent predictors of death in patients awaiting liver transplantation [83]. Evidence has suggested that elimination of risk factors for post-transplant metabolic syndrome may significantly increase the survival of patients suffering from NASH [71]. There was no significant difference in the short-term or long-term survival of patients who developed de novo NAFLD [36].

Previously, some authors had suggested that in patients with NASH, there tend to be more frequent mortality in the early postoperative period (30–90 days after liver transplantation) [64, 74] and one year after surgery [64] than inpatients suffering from other liver diseases.

In most publications, it has been noted that post-transplant mortality is comparable to or even lower for patients with NASH than patients with other diseases. For example, the University of Miami compared the results of liver transplantation for NASH-related cirrhosis and alcoholic cirrhosis. There was no significant difference in survival between the groups. Sepsis was the leading cause of posttransplant death in both groups, followed by cardiovascular conditions (P = 0.21). Recurrent steatohepatitis (33% *vs* 0%, P < 0.0001) and acute rejection (41% *vs* 23%, P < 0.023) were much more common in the NASH group than in the alcoholic cirrhosis group. However, these complications did not lead to higher rates of liver retransplantation. There was no difference in graft failure between the groups (P = 0.3973) [78].

Four international centers (in Australia, USA, UK and Italy) conducted a joint study of morbidity and mortality in 247 patients with NAFLD with progressive liver fibrosis or cirrhosis. Patients with NAFLD with progressive fibrosis or cirrhosis had lower rates of liver-related complications and hepatocellular carcinoma than corresponding patients with HCV infection, but similar overall mortality [84].

In the United States, from January 1, 1997 to October 31, 2010, the posttransplant survival of patients with NASH (n = 1810) at 1 (87.6%), 3 (82.2%) and 5 years (76.7%) was higher than the survival of patients with hepatocellular carcinoma, hepatitis C virus, alcoholic liver disease, acute hepatic necrosis, hemochromatosis, or cryptogenic liver disease. It was only lower than the survival of patients with primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis, or hepatitis B virus [73].

X. Wang et al. [85] showed that survival and long-term outcomes of liver transplantation in NASH-related cirrhosis are similar to those in cirrhosis related to alcoholic liver disease and HCV. According to these authors, since patients with NASH have a greater risk of death from cardiovascular complications or sepsis after liver transplantation, closer attention by clinicians and more aggressive therapy for these complications are required.

In recent years, graft survival among recipients of deceased donor and living donor livers continued to improve [66]. Therefore, within this period, the overall post-transplant survival of patients with NAFLD became not only comparable to the survival of patients suffering from other diseases [18, 67, 73], but also higher than the survival of patients suffering from HCV and alcoholic liver disease (P < 0.001) [75]. On average, one-year post-transplant survival is approximately 79–90%, the three-year survival is 82–83%, and the five-year survival is 72–78% [64, 70, 75]. The liver retransplantation outcomes for NASH-related cirrhosis are significantly worse than with cirrhosis of other etiologies [76].

Previously, the cause of post-transplant death in patients with NASH was primarily infection (57.1%), which is significantly higher than in other liver diseases [64]. In more recent studies, the leading causes of mortality were cancer (25%), infectious complications (25%), and cardiovascular disease (21.9%). Only 9% of deaths were associated with post-transplant cirrhosis [65]. Patients with NASH have a high risk of death from cardiovascular complications, which, according to J. Merola et al. [71], is a leading cause of post-transplant mortality.

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