Skladaný Ľubomír, Badinková Jana, Adamcová Selčanová Svetlana. Non-alcoholic fatty liver disease after liver transplantation: A lifestyle reloaded. Journal of Education, Health and Sport. 2017;7(10):116-133. eISSN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.1000968
http://ojs.ukw.edu.pl/index.php/johs/article/view/4961

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part B item 1223 (26.01.2017).
1223 Journal of Education, Health and Sport eISSN 2391-8306 7

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 15.09.2017. Revised: 10.10.2017. Accepted: 10.10.2017.

NON-ALCOHOLIC FATTY LIVER DISEASE AFTER LIVER TRANSPLANTATION: A LIFESTYLE RELOADED

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ABSTRACT:

BACKGROUND AND AIMS. Apart from non-alcoholic steatohepatitis (NASH) as the sole etiology behind liver transplantation (LTx), non-alcoholic fatty liver disease (NAFLD)/NASH can play an important role in all the remaining etiologies of LTx. To gauge such a contribution of NAFLD/NASH, authors made use of 2 assumptions: a) there is tendency post-LTx to regain body shape (including obesity and its metabolic consequences) patients (pts) had before decompensation of their liver disease, therefore b) post-LTx fatty liver index (FLI) ≥ 60 (sensitivity/specificity for NAFLD>85%) might reflect NAFLD pre-LTx.

METHODS. a) A retrospective study of body mass index (BMI) in the 6th and 12th moths (m) after LTx, b) a cross-sectional study of FLI (and ultrasonography) > 6 m after LTx (Jana Badinková (JB), october 2015). a) An analysis of the medical records of pts after LTx performed in transplantation centre (TC) Banska Bystrica (BB). *Interval studied:* January 2011 – march 2016 (JB). *Source of data:* Hospital Information System (Care Centre® Copyright 2000, CGM, Version 3.33.2). *Inclusion criteria:* LTx in TC BB > 6 m ago. *Exclusion criteria:* LTx due to NASH; insufficient data for a FLI calculation. b) All the pts

selected by inclusion/exclusion criteria were contacted by a TC physician (JB) via mobile phone (text message, or phone call) in order to determine current waist circumference. *Recorded variables:* gender; age; etiology of advance chronic liver disease; BMI; ultrasonography; FLI (triacylglycerides, gamma-glutamyltransferase, waist circumference (cm), height (m), weight (kg)). Overweight was defined as a BMI > 25 kg/m^2, obesity as a BMI > 30. An FLI > 60 was the value that indicated NAFLD.

RESULTS. From January 2011 to December 2015, 90 pts underwent LTx in TC BB. The inclusion criteria were met by 87 of them, 40 pts were subsequently excluded. The cohort for final analysis consisted of 47 pts. Average age – 51 years (22-65); women - 25 (53%); indications for LTx: alcoholic liver disease – 22 pts (46%), autoimmune hepatitis - 7 pts (15%), primary sclerosing cholangitis – 6 pts (13%), primary biliary cholangitis - 5pts (11%), chronic hepatitis C – 3 pts (6,5%), chronic hepatitis B - 3pts (6,5%), other – 1 pt (2%). Average time from LTx to FLI measurement was 33 m (6-53). Overweight, and obesity 6 m after LTx: 22 pts (47%), and 5 pts (11%), respectively; 12 m after LTx - 21 pts (45%), and 9 pts (19%), respectively. FLI > 60 was found in 20 pts (43%). Twelve of 20 pts (60%) with FLI > 60 had an ultrasonography without the signs of steatosis.

CONCLUSIONS. Provided the validity of assumptions that a) LTx restores pre-LTx-pre-decompensation body shape, and therefore b) FLI post-LTx is similar to FLI pre-LTx-pre-decompensation, the real contribution of NAFLD/NASH to LTx burden could be much greater than that derived from isolated NASH-LTx numbers. In this small cohort of pts transplanted for non-NASH etiologies, pre-LTx NAFLD could have been present in as much as 43% of pts.

KEYWORDS: NAFLD – non-alcoholic fatty liver disease; LTx - liver transplantation; BMI – body mass index; FLI – fatty liver index; lifestyle

INTRODUCTION

The Burden of liver cirrhosis, in clinical practice recently referred to as advanced chronic liver disease (ACLD), has been increasing over the past 2 to 3 decades (1, 2). In terms of mortality caused by ACLD, Slovakia ranks fourth or fifth in Europe, and the trend is incerasing (2, 3, 4). Non-alcoholic fatty liver disease (NAFLD) and its more progressive form, non-alcoholic steatohepatitis (NASH), are among the most significant driving forces behind this trend; the burden of NAFLD/NASH is composed of ACLD, but also of hepatocelullar carcinoma (HCC), and - above all - cardiovascular events (5, 6, 7, 8).

The Increasing prevalence of NAFLD/NASH has been attributed to an increasing incidence of its major risk factors - overweight, obesity, metabolic syndrome (MS), and diabetes mellitus type 2 (T2DM); all of them are mainly mediated by a so-called western lifestyle, characterized by three main domains: a sedentary lifestyle, inactivity, and excessive intake of dietary energy (9, 10, 11, 12, 13, 14, 15, 16). For example, between the years 1980 and 2009, the number of people with T2DM in Slovakia increased from 120,000 to 337,000 1(17). The link between T2DM, overweight, and obesity is so strong, that a new term "Diabesity" was introduced; also, diabesity has been characterized as a pandemy (18). The overweight, obesity, MS and T2DM, are a risk factors for the emergence of NAFLD: NAFLD can be found in at least 25-30% of the so-called general population (19, 20, 21, 22), in 67% of overweight pts, in 94% of obese patients (pts), (20), in 70-90% of pts with MS (23), and in > 50% of pts with T2DM (24). Moreover, NAFLD is afflicting 3-10% of children, and as much as 40-70% if they are obese (25). These high figures has led to the question how strongly affected is the cohort of pts with various chronic liver diseases (CLD) other than NAFLD/NASH; it seems well substantiated to suppose that there could be a diffusion of NAFLD to pts with CLD of any etiology, including the patients after liver transplantation (LTx).

Diagnosing NAFLD. In a scientific literature, the diagnosis of NAFLD was based on the a) exclusion of the other causes of CLD, and on b) confirming a fatty degeneration in a liver biopsy specimen (the minimum criterion being >5% steatosis) (3, 26, 27). It is well-known, and vital for this study, that the histological picture of NAFLD tend to disappear at the cirrhotic stage of ACLD (the so-called burned-out phase of NAFLD, including in the liver explants acquired during LTx) (28). It is one of the main reasons for the notion, that the rate of NAFLD within the ACLD and LTx cohorts culd be seriously underestimated (26). As a non-invasive methods for the diagnosis of NAFLD and NASH are beginning to be put into daily clinical practice, more light could be shed on the possible underdiagnosis of NAFLD in pts with other etiologies of CLD (3). The noninvasive diagnostic methods for NAFLD differ in their accuracy and availability; from the list of a more frequently used ones, the Fatty Liver Index (FLI, with a sensitivity of 87% and specificity of 86%), was used in this study (Tab. 1) (29).

Liver Transplantation and NAFLD. In contrast to alcoholic liver disease (ALD), the mitigation of risk factors that resulted in NASH, is not required before LTx – i.e. pts suffering from an inactivity and a diet with excessive amount of energy are not required to achieve any relevant change before LTx (26). This leads to the on-going activity of these risk factors after

LTx; moreover, they are often more intensive than before LTx (26, 30). We named this clinical context lifestyle matrix reloaded. Although the results of around a dozen studies are not unequivocal in this regard, it is accepted that the survival after LTx is worse with NAFLD than with other etiologies (31, 32, 33). Post-transplant NAFLD has been classified to two main types – a *recurrence* (if the LTx was indicated for NASH), and a *de-novo* NAFLD (occurring in the patients transplanted for a non-NASH CLD (21) (Tab. 2):

1. Recurrence of NAFLD/NASH after LTx was first documented in 1992 (34, 35, 36). According to the registries in the USA and Europe, with the growth of 170% between 2004-2013, NASH has become *the fastest growing indication for LTx*, and in US it has been recently declared to be the most common one (37, 38, 39, 40). In the Transplantation Centre Banská Bystrica (TC BB), NASH was the cause of LTx in 15 cases of 189 LTx (8%) (Update to October 11 th 2017). *The frequency* of NAFLD/NASH recurrence after LTx varies according to how and when it was diagnosed: from <10% during the first 6 months (m) after LTx, to up to 100% after 10 years (21, 26, 41, 42). The occurrence of NAFLD is related to the activity of a risk factors; as a matter of the fact, in the pivotal studies on NAFLD after LTx, the average body mass index (BMI) varied from 29 to 35 kg/m^2 (26, 33, 36, 44), and the prevalence of T2DM from 23% to 53% (26, 33, 36, 44). *The natural course* of the recurrent NAFLD is often progressive (21) – with steatohepatitis occuring in 4%-33% after a period of 6-12 months (26), and advanced fibrosis in up to 33% after 4-120 months (26, 45). Of note, cardiovascular morbidity and mortality in recurrent NALD exceeded the hepatic one by several orders (26, 44).

2. *De-novo* NAFLD emerges after LTx indicated for non-NASH etiology of CLD (Tab. 2) (36, 46, 47). *The risk factors of de-novo NAFLD* are related to the recipient, graft, and environmental factors (21, 48). Besides the characteristics of the graft steatosis and genetics, and of an immunosuppression, however, (49), the risk factors for *de-novo* NAFLD *are the same as in the general population* - i.e. overweight, obesity, MS and T2DM; however, their prevalence is higher in the cohort after LTx, they tend to accumulate, and hit with a greater intensity than in the general population (21, 30, 50). The effect of the standard immunosuppression used after LTx is associated with an increased risk of T2DM, dyslipidaemia, and the pathogenesis of NAFLD (51, 52, 53, 50). *Based on histological findings, the occurrence* of *de-novo* NAFLD is 18-34% (21, 42, 49, 54, 55). In a histological study by Hejlová et al. from IKEM Prague, the presence of NAFLD was demonstrated in 30% of 548 pts after 1 year (y), and in 48% after 10 ys (42). The prognosis of *de-novo* NAFLD/NASH is more favourable than that of a recurrence (21, 26).

When a sufficient number of pts from TC BB reached the stage of clinical stability, it was noticed that a large proportion of them suffered overweight, obesity, MS and T2DM – i.e. the risk factors of NAFLD (Tab. 2) (35, 49, 54). Their lifestyle and ensuing physical proportions begun to resemble those before LTx (and before the decompensation of ACLD); the suspicion was subsequently corroborated by lifestyle questionnaires. In some of them, NAFLD was diagnosed and, in cases of non-NASH indications for LTx, it was named *de-novo* NAFLD. Gradually, a question arose if the so-called *de-novo* NAFLD was not in fact present (unrecognized) before a LTx. (Fig. 1). If so, significant number of post-LTx NAFLD cases would have to be re-classified from a *de-novo* to reccurences and, no less importantly, the overall burden of pre-LTx NAFLD re-calculated.

AIM

To determine the prevalences of overweight, obesity, and FLI as a surrogate markers of (*de- novo*) NAFLD – with the intent to shed a light on the possibility of an unrecognized pre-LTx NAFLD.

PATIENTS AND METHODS

a) A retrospective study of BMI in the 6th and 12th m after LTx, b) a cross-sectional study of FLI (and ultrasonography [US]) > 6 m after LTx (Jana Badinkova (JB), october 2015). a) An analysis of the medical records of pts after LTx performed in TC BB. *Interval studied:* January 2011 – march 2016 (JB). *Source of data:* Hospital Information System (Care Centre® Copyright 2000, CGM, Version 3.33.2). *Inclusion criteria:* LTx in TC BB > 6 m ago. *Exclusion criteria:* LTx due to NASH; insufficient data for a FLI calculation. b) All the pts selected by inclusion/exclusion criteria were contacted by a TC physician (JB) via mobile phone (text message, or phone call) in order to determine current waist circumference (WC). *Recorded variables:* gender; age; ACLD etiology; BMI; US; FLI (triacylglycerides [TAG], gamma-glutamyltransferase [GMT], WC [cm], height [m], weight [kg]). Overweight was defined as a BMI > 25 kg/m^2, obesity as a BMI > 30 (56). A FLI > 60 was the value that indicated NAFLD (57).

RESULTS

From January 2011 to December 2015, 90 pts underwent LTx in TC BB. The inclusion criteria were met by 87 of them, 40 pts were subsequently excluded. The cohort for final analysis consisted of 47 pts (Graph 1). Average age – 51 ys (22-65); women - 25 (53%); indications for LTx: ALD – 22 pts (46%), autoimmune hepatitis (AIH) - 7 pts (15%), primary sclerosing cholangitis (PSC) – 6 pts (13%), primary biliary cholangitis (PBC) - 5pts (11%), chronic hepatitis C (CHC) – 3 pts (6,5%), chronic hepatitis B (CHB) - 3pts (6,5%), other – 1

pt (2%) (Graph 2; Tab.3.). Average time from LTx to FLI measurement was 33 m (6-53). Overweight, and obesity *6 m after LTx*: 22 pts (47%), and 5 pts (11%), respectively; *12 m after LTx* - 21 pts (45%), and 9 pts (19%), respectively (Graph 3). FLI > 60 was found in 20 pts (43%) (Graph 1). Twelve of 20 pts (60%) with FLI > 60 had an US without the signs of steatosis.

DISCUSSION

This pilot study, focusing on the so-called *de-novo* NAFLD after LTx, suffered several shortcomings: a retrospective design, limited number of pts, and a rather speculative nature of the implication that FLI measured after LTx could be reflective of the presence of NAFLD not only at the time of measurement but, by the the analogy derived from the similarities between pre- and post-LTx lifestyles and body shapes, also of the possible NAFLD before LTx. The theory behind this notion has been named Lifestyle Matrix Reloaded; the behaviour of its biomarkers, such as BMI evolution long before- and after LTx, are strongly supportive of its validity – i.e. of the re-adoption of a pre-LTx lifestyle. Our data on overweight (6m > LTx 47%, 12m 45%), obesity (6m 11%, 12m 19%), and FLI-derived prevalence of *de-novo* NAFLD (43% at 33 m), correlate well with the data from the literature and are considereed to be a true reflection of the morbidity in our cohort (21, 42, 49, 54, 55). The reasons for such a high rates will be the subject of further examination. However, it can be already safely assumed that the most important unifying cause is represented by the cumulative impact of a tripple hit – a sedentary lifestyle, inactivity, and a western-type diet (21, 30, 50). This notion has been supported by Szántová et al., who tested 923 outpatients of liver and gastroenterology clinics, and have found overweight and obesity in 59%, and inactivity in 68% of the participants (15). The prevalence of the so-called *de-novo* NAFLD 33 m after LTx (43%) according to the FLI would fall to the right side of the interval from the literature: Seo - 18%, Hejlová - 30%, Sprinzl - 34%, Dumortier - 49%, Vallin 67% (21, 42, 49, 54). The correlation between the FLI and US in diagnosing NAFLD in our pts was poor (40%). It is difficult to comment on this discrepancy, because it was not the endpoint of the study, and because there is little data fulfilling all the necessary criteria for a comparison – i.e., the post-LTx setting, inclusion of the whole spectrum of steatosis (especialy a mild forms), a systematic use of both methods, and the use of a golden standard – histology or, more recently, magnetic resonance spectroscopy (58, 59). This aspect will be investigated in a prospective study, which is underway. We were not able to retrieve a pre-LTx waist circumference measurements, which precluded direct comparison of pre- and poist-LTx FLI. Therefore, the intention of this study was to make an indirect comparison and achieve at least

some insight into the possibility of a presence of undiagnosed NAFLD before the LTx. FLI appeared to be an ideal tool for this purpose, since its components could bear a remote reflection of the pre-LTx situation. As for the post-LTx phase, a FLI is considered to be a reliable marker of NAFLD (Fig. 1). It is the opinion of the authors, that the possible contribution to the post-LTx NAFLD of a graft steatosis, graft genetics, and immunosuppression, does not outweight the steatogenic effect of the lifestyle (reloaded) (60, 61, 62).

CONCLUSIONS

For the patients, the sobering personal experience of LTx is not a sufficient protection against a detrimental health effects of a western-type lifestyle after LTx; according to FLI, 43% of stable pts 33 months after LTx could develop *de-novo* NAFLD. Since their lifestyle and body shape at the time of FLI measurement were often similar to the pre-LTx, pre-morbid period, we hypothesize that NAFLD could have coexisted with their CLD of other etiology. This would mean that their post-LTx NAFLD would in fact be recurrence, and not a *de-novo* NAFLD. A possible consequences of this reclassification would me several-fold; the most important for our centre would be focusing on pre-LTx lifestyle intervention in all pts, not only in those with NAFLD.

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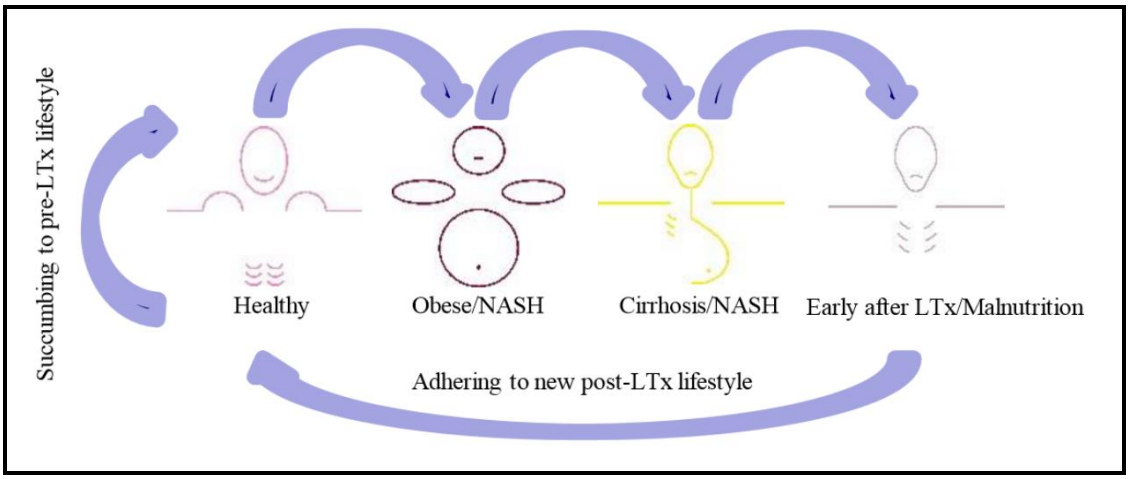
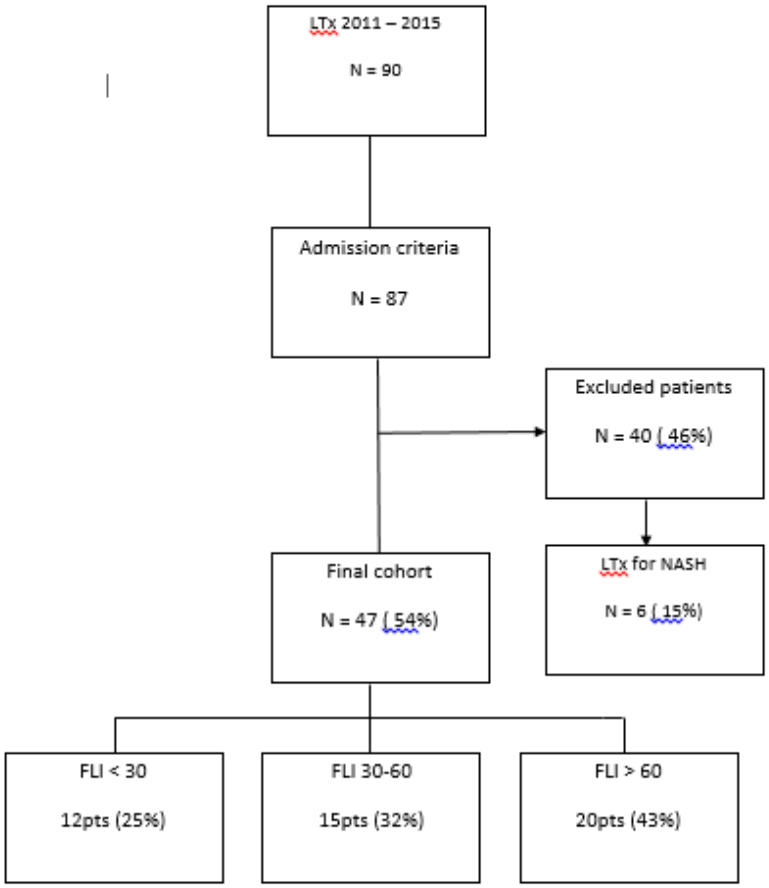
Figure 1. Circulus vitiosus of somatotype of patients with CLD

(CLD = chronic liver disease; LTx = liver transplantation; NASH = non-alcoholic steatohepatitis)



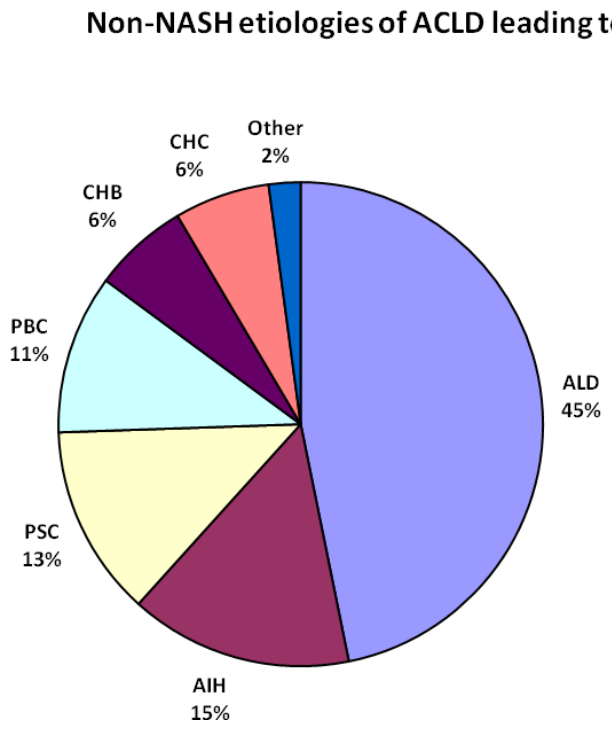
Graph 1. Flowchart of the study

(LTx = patients, who were transplanted; NASH = non-alcoholic steatohepatitis; FLI = fatty liver index; pts = patients)



Graph 2. Non-NASH etiologies of ACLD leading to liver transplantation

(ACLD = advanced chronic liver disease (new name for cirhosis); NASH = non-alcoholic steatohepatitis; non-NASH ACLD = other etiology of ACLD than non-alcoholic steatohepatitis; LTx = liver transplantation; ALD = alcoholic liver disease; AIH = autoimune hepatitis; PSC = primary sclerosing cholangitis; PBC = primary biliary cholangitis; CHC = chronic hepatitis C; CHB = chronic hepatitis B; other = other etiology of ACLD)



Graph 3. Overweight and obesity after LTx accordig to BMI
(BMI = body mass index; LTx = liver transplantation; 6m = 6.months after liver transplantation; 12m = 12.months after liver transplantation)

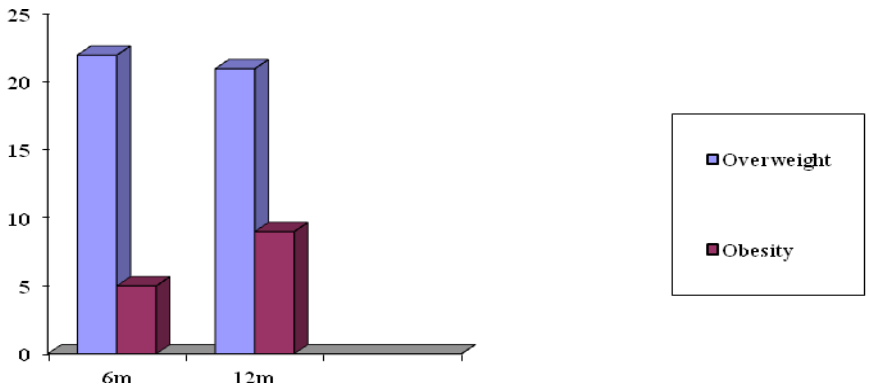


Table 1. Non-invasive diagnostic modalities for NAFLD and NASH

(NAFLD = non-alcoholic fatty liver disease; NASH = non-alcoholic steatohepatitis; MS = metabolic syndrom; T2DM = type 2 diabetes mellitus; TAG = triglycerids; GMT = gamaglutamyltransferasis; ALT = alaninaminotransferasis; BMI = body mass index; FLI = fatty liver index; LAP = lipid accumulation product; US = ultrasonography; US-FLI = ultrasonographic fatty liver index; CAP = controlled attenuation parameter; CT = computer tomography; CT-LP = liver parenchyma attenuation (normal range 50 – 57 HU); CT-LS = liver to spleen attenuation difference (normal range 8-10HU); CT-L/S = liver to spleen attenuation ratio; MR spectroscopy = magnetic resonance with spectroscopy of liver; α-2-MG = α2-macroglobulin; apo-A1 = apolipoprotein A1; CK18 = cytokeratin 18 fragments; y = years; μg = nanogram; l = liter; * = limited)

	Name of the test	Constituents	Senzitivity	Specificity	Local availability
1	2	3	4	5	6
NAFLD	Steatotest	α2-MG, haptoglobin, apo-A1, bilirubin, GMT, fasting glucose, TAG, cholesterol, ALT, age, gender, BMI	90%	70%	No
	FLI	Height, weight, waist circumference, GMT, TAG	87%	86%	Yes*
	NAFLD liver fat score	MS, T2DM, insulin, AST, ALT	95%	95%	Yes
	LAP	Waist circumferences, TAG, gender	77-82%	75-79%	Yes
	US		60-94%	66-97%	Yes
	US-FLI		46%	50-57 %	No
	CAP		79%	71%	No
	CT	CT-LP CT-LS CT-L/S	52% 60% 82%	100% 100% 100%	Yes
	MR spectroscopy		92-100%	92-97%	Yes*
NASH	HAIR	Hypertension, increased ALT, insulin resistance	80%	89%	Yes*
	Palekar's score	Age ≥ 50y, female gender, BMI ≥ 30, AST/ALT ≥ 0,8, plasma levels of hyaluronic acid ≥ 55μg/l	74%	66%	Yes*
	NASH test	α2-MG, haptoglobin, apo-A1, bilirubin, GMT, ALT, AST, TAG, cholesterol, age, gender, height, weight	33%	94%	No
	Gholam's model	AST, diabetes mellitus	83%	82%	Yes

1	2	3	4	5	6
	NASH diagnostics	CK18, adiponectin, resistin	72%	91%	No
	NASH diagnostic panel	Diabetes mellitus, gender, BMI, TAG, antigens M30 a M53	91%	92%	No
	Apoptosis panel	CK18, soluble Fas and Fas ligands	84%	89%	No
	Nice model	ALT, CK18, MS	84%	86%	No

Table 2. Indications for liver transplantation and current numbers on Transplant Centre Banska Bystrica

(NASH = non-alcoholic steatohepatitis; Non-NASH = other indication for liver transplantation than non-alcoholic liver disease; pts = patiens; TC BB = Transplantation centre Banska Bystrica; * = disease, which have steatosis in their picture)

Etiology of liver disease			Number of pts in TC BB
NASH			15
Non-NASH	1. Non-cholestatic hepatitis	Alcohol liver disease * Autoimmune hepatitis Chronic hepatitis C * Chronic hepatitis B Cryptogenic liver disease	77 19 11 3 2
	2. Cholestatic hepatitis	Primary biliary cholangitis Primary sclerosing cholangitis Secondary biliary cirrhosis Biliary atresias Alagill's syndrom Non-syndromatic paucity of intrahepatal bile ducts Progresssive familiary intrahepatal cholestasis Cystic fibrosis Caroli disease	13 - 14 - - - 2 - 1
	3. Metabolic disease	Alfa-1-antitrypsin deficiency Hereditary hemochromatosis* M.Wilson * Tyrosinemia Glykogenosis IV.type Neonatal hemochromatosis Ornithin transcarbamylase deficiency	- - 2 - 1 - 1
	4. Liver tumors	Primary hepatoma Primary hepatoblastoma Epitheloid hemangioendothelioma Carcinoid	- 20 - 1

	5. Metabolic disease with hard disability of extrahepatal organs	Amyloidosis Hyperoxaluria Hyperlipoproteinaemie*	2 - -
	6. Other disease	Budd-Chiari syndrom Polycystic disease Echinococcus cyst	- 1 1

Table 3. Baseline characteristics (N = 47)

(N = total number of analysed patients; ACLD = advanced chronic liver disease, new name for liver cirrhosis; ALD = alcoholic liver disease; AIH = autoimmune hepatitis; PBC = primary biliary cholangitis; PSC = primary sclerosing cholangitis; CHC = chronis hepatitis C; CHB = chronic hepatitis B; LTx = liver transplantation)

Monitored variables	**N = 47**
Gender (Male/Female)	22/25 (47%/53%)
Age (years)	51 (22 –65)
Etiology of ACLD	
ALD	22 (46%)
AIH/PSC/PBC	(7/6/5) (15%/13%/11%)
CHC/CHB	3/3(6%/6%)
Other	1 (2%)
Time from LTx to analysis (months)	33 (6-53)