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# Liver diseases in the general population – the importance of active screening

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**A** – Study Design, **B** – Data Collection, **C** – Statistical Analysis, **D** – Data Interpretation, **E** – Manuscript Preparation, **F** – Literature Search, **G** – Funds Collection

**Summary** **Background.** Chronic liver diseases are the 5th most common cause of death in Slovakia overall, and in the case of productive age, they are in 3rd place after cardiovascular and oncological diseases. The most common liver diseases in Slovakia include: alcoholic liver disease with its various stages (alcoholic hepatitis to liver cirrhosis), viral liver diseases and non-alcoholic fatty liver disease.
**Objectives.** To determine the incidence of liver diseases in a sample of general population from the Bardejov district and, based on the findings, to draw recommendations for general practitioners regarding the need for liver disease screening in their clinics.
**Material and methods.** During the "Week of Healthy Liver" event, we examined a total of 179 people (126 women and 73 men). The average age of the examined patients was 52.6 years (± 13.3 years). The participants had an opportunity to have their blood pressure, pulse, waist circumference and hip circumference measured. They could also be measured on a Tanita scale, have capillary blood samples for antibodies against hepatitis B, C and venous blood for a biochemical spectrum (15 indicators) taken, undergo a transient elastography examination and percentage measurement of fat in the liver.
**Results.** The average BMI of the participants was 27.8 (± standard deviation 6.35). 66% of the participants were overweight and obese. Via transient elastography, we found the presence of fibrosis in 20.5% of the participants; up to 59% of the patients had fatty liver (S1–S3). In the group of patients without detected liver fibrosis (135/170), we detected steatosis of grade 1–3 (S1–S3) in 73/135 patients (54%) of the group. We analysed the connections between the occurrence of fibrosis and steatosis of the liver and other examined laboratory parameters (including laboratory ones). We processed the results statistically.
**Conclusions.** NAFLD provides a large field of action for interventions by general practitioners. In overweight and obese patients, NAFLD screening should be performed with a focus on measuring blood pressure, weighing the patient, measuring the waist and hips circumference, determining the level of cholesterol, liver function tests, blood glucose levels and the patients should be sent for an ultrasonographic examination of the abdominal cavity. These examinations can also be carried out during the patient's preventive examination, which is reimbursed by health insurance companies once every 2 years. The position of general practitioners in the screening and management of liver diseases is irreplaceable.
**Key words:** liver diseases, non-alcoholic fatty liver disease, viral hepatitis, transient elastography, liver disease screening.

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## Background

Chronic liver diseases are the 5th most common cause of death in Slovakia overall, and in the case of productive age, they are in 3rd place after cardiovascular and oncological diseases [1]. The burden of the chronic disease [2] is most recognized in case of patients living with cardiovascular conditions [3] limiting their abilities and demanding long-run compliance to therapeutic schemes [4], or disorders manifesting with pain [5] or dyspnoea [6], which is in contrast to the liver diseases that stay silent, and thus undetected and thus untreated, for a considerable time. The most common liver diseases in Slovakia include: alcoholic liver disease with its various stages (alcoholic hepatitis to liver cirrhosis), viral liver diseases and non-alcoholic fatty liver disease [1], out of which the premature mortality due to alcohol-related diseases tend to draw the focus of the public [7].

NAFLD – Non-alcoholic fatty liver disease – is the most common chronic liver disease in economically developed countries [8]. It includes a wide spectrum of liver diseases: from simple steatosis of the liver to steatohepatitis, fibrosis and liver cirrho-

sis. The worldwide prevalence of NAFLD is reported to be around 25% in adults [9], while it is higher in patients with metabolic syndrome [10]. In children, the prevalence of NAFLD is related to the child's age: 3–10%, but in obese children it reaches 40–70% [11].

In Europe, 73 million people had NAFLD in 2016, of which 2.5 million had advanced fibrosis. By 2030, the NAFLD cases number can be expected to increase to 84 million. The alarming assumption is that by 2030 the number of people with advanced fibrosis will double in Europe – from 2.5 million to 5 million [12]. Lifestyle-related chronic liver diseases become common in ageing populations, adding to the rising the cost of healthcare [13] and prolonged hospitalisations [14]. They negatively influence overall fitness of human organism and may impair cognitive functions, altering capacity to make informed decisions [15]. They also add to health hazards associated with other illnesses [16]. Therefore, it is crucial to educate the public [17] about the risks associated by diseases preventable by vaccinations [18, 19], like influenza or COVID-19, in order to preven both directly in the vulnerable patients and the persons surrounding them, including medical personnel [20, 21].

Risk factors for the development of NAFLD are: obesity, type 2 diabetes mellitus (DM), hypertriglyceridemia [22, 23].

Viral liver diseases (chronic hepatitis B, chronic hepatitis C) are, along with metabolic diseases (NAFLD), considered to be the most common liver diseases [24, 25].

Chronic hepatitis C (CHC) goes on for a long time without symptoms or with only minimal manifestations, which are mostly attributed to other causes, as well as is possible increased activity of aminotransferases, which often only minimally exceeds the upper limit of physiological values [26]. The risk of liver cirrhosis is 15–30% after 20 years of present HCV infection. Each year, 1–3% of patients with cirrhosis progress to HCC [27].

The World Health Organization has adopted a global strategy to eliminate viral hepatitis as a major public health threat by 2030. This strategy covers both hepatitis B (HBV) and hepatitis C (HCV). Its goals include a 90% reduction in the consequences and a 65% reduction in mortality due to HBV/HCV by 2030.

## Objectives

To determine the incidence of liver diseases in a sample of general population from the Bardejov district and, based on the findings, to draw recommendations for general practitioners regarding the need for liver disease screening in their clinics. On 24.04–28.04.2023, an institutional project of the Slovak Society of Practical Obesitology and the town of Bardejov (no. 3883/2023) under the name "Week of Healthy Liver" took place in the premises of the Polish-Slovak House in Bardejov. The Polish-Slovak House, the Regional Public Health Office with the seat in Bardejov, the Remedium s.r.o. polyclinic in Bardejov Spa and the Faculty of Public Health Studies of the Slovak Medical University with headquarters in Bratislava participated in the project. The Week of Healthy Liver culminated on 28.04.2023 with an afternoon block of educational lectures for residents of Bardejov and the surrounding area.

## Material and methods

During the "Week of Healthy Liver" we examined a total of 179 people (126 women and 73 men). The average age of the examined patients was 52.6 years (± 3.3 years). The participants had an opportunity to have their blood pressure, pulse, waist circumference and hip circumference measured and to have the measurements on a Tanita scale taken.

The *Tanita SC-240 MA* scale is a portable body analyzer that has a weighing capacity of 200 kg and accuracy of 100 g. It works on the principle of bioelectrical impedance, which determines body fat content by calculation after measuring body resistance. The resistance of the body changes according to the content of fat and water [28]. Muscle tissue is significantly more hydrated than fat tissue, and this property is used in the calculation of fat content. The calculation of the fat percentage is based on the measured resistance, measured weight, entered height and gender. The device is equipped with 2 electrodes on the footplates [29].

The Tanita scale allows to determine a number of parameters during one measurement: weight, BMI (body mass index), body fat in %, body fluid in %, visceral fat, adipose tissue in kg, lean tissue in kg, muscle mass, body fluid in kg, basal metabolic rate, bone mass and metabolic age.

After signing the informed consent, the patients were examined for antibodies against hepatitis B and hepatitis C from the capillary blood using a rapid diagnostic test (Turklab rapid diagnostic test).

From the venous blood, we examined the biochemical spectrum on the *Celercare M5 MNCHIP analyzer* (we examined the glycemic level, fat spectrum – CHOL, TAG – triacylglycerols, HDL – high density lipoprotein, LDL – low density lipoprotein, AST – aspartate aminotransferase, ALT – alanine aminotransferase, GGT – gammaglutamyltransferase, ALP – alkaline phosphatase, creatinine, uric acid, total proteins, albumin, total and conjugated bilirubin).

The results of biochemical parameters as well as of capillary blood samples were ready within 15 minutes. All subscriptions were anonymous.

After taking the samples, the patients could undergo an examination on the Fibroscan device. We used the method of *transient elastography (TE)* which is a non-invasive painless method that measures liver stiffness. The principle of elastography is based on a finding that a fibrotic liver is less deformable by the action of an external forces, i.e. it is less elastic, compared to a normal liver [10]. It evaluates the speed of shock waves as they travel through the liver. It is used to assess a degree of liver fibrosis (according to the METAVIR classification), in chronic hepatitis B and C, chronic cholestatic diseases, alcoholic liver disease, non-alcoholic fatty liver disease, autoimmune hepatitis. With high accuracy it confirms or refutes cirrhosis. The results are given in kPa.

The device had a built-in special software for quantifying the presence of steatosis (the so-called CAP module – controlled attenuation parameter).

CAP measurement results are given in dB/m. The measurement range is from 150 dB/m to 400 dB/m. We distinguish the degrees of fatty liver according to the percentage of liver damage as follows: S0: 150–240, S1: 240–270, S2: 270–303, S3: 303–400. There are accurate scales for evaluating fatty liver not only for NAFLD, but also for viral hepatitis and liver diseases of various etiologies [30, 31].

The patients had an opportunity to consult the results of their blood samples and the Fibroscan examination with a doctor and public health workers, and received educational materials and recommendations regarding the next procedure. For patients who have been diagnosed with liver damage, we have suggested an examination in our outpatient clinic at the Remedium s.r.o. polyclinic.

We also gave the patients questionnaires regarding their health literacy about liver diseases and screening for obstructive sleep apnoea syndrome. At the same time, we wanted to find out if there is a correlation between the degree of fibrosis and steatosis of the liver and the presence of sleep apnoea syndrome. Due to the scope of the text, we will describe these results in a next publication.

## Results

During the "Week of Healthy Liver" we examined a total of 179 people (126 women and 73 men). The average age of the examined patients was 52.6 years (± 13.3 years). The average BMI of the participants was 27.8 (± standard deviation 6.35). 66% of the participants were overweight and obese. The measurement on the Tanita scale showed that total fat was in-

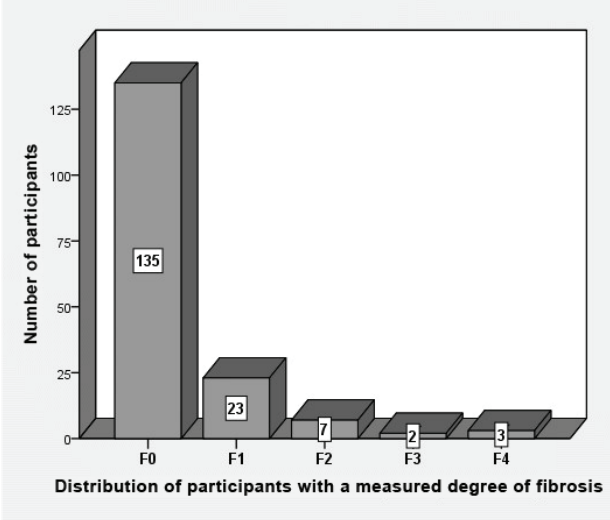


**Figure 1.** Distribution of the occurrence of liver fibrosis in the participants of the measurements

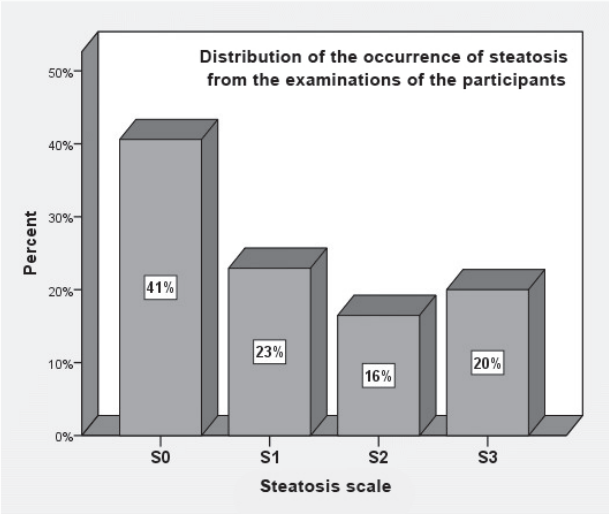


**Figure 2.** Occurrence of liver steatosis in the participants of the measurements

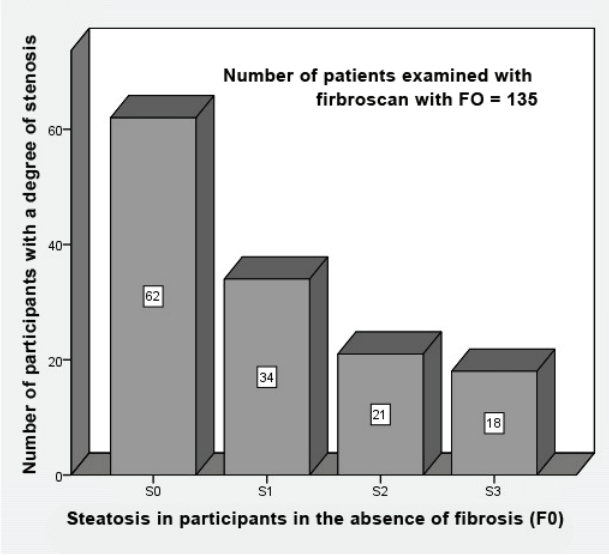


**Figure 3.** The presence of hepatic steatosis in patients without fibrosis

creased in 56% of the measured participants, visceral fat was increased in 20%. Via transient elastography we determined the presence of fibrosis in 20.5% of the participants, which is shown in Figure 1. This means that every fifth randomly examined person had liver damage! Fortunately, more advanced liver fibrosis (F2–F4) accounted for only 7%. When we analysed the presence of liver steatosis, we found that up to 59% of patients had fatty liver (S1–S3) – more detailed results are shown in Figure 2.

23% of the participants had grade 1 steatosis, 16% had grade 2 steatosis, and 20% had grade 3 steatosis. We were interested in the presence of fatty liver in the group of patients without detected liver fibrosis (stage F0) – 135/170 (79.4%). The results are shown in more detail in Figure 3.

62/135 (45.9%) patients had steatosis grade S0 (0–10% fatty liver), 34/135 patients (25.2%) had S1 steatosis (11–33%), 21/135 patients (15.6%) had S2 steatosis (34–66%) and 18/135 patients (13.3%) had S3 steatosis (67–100%). Our analysis shows that despite the absence of liver fibrosis, fatty liver of various degrees (S1–S3) was present in 54.1% of the measurement participants!!! There is a huge space for the preventive action of primary care physicians to appeal to the need for a healthy diet and regular physical activity in the population, even in the context of non-alcoholic fatty liver disease.

As part of our analysis, we were seeking the connections between the occurrence of fibrosis and steatosis of the liver and other examined laboratory parameters (including laboratory ones). We wanted to assess the sensitivity, specificity and validity of the tests used in fibrosis (F) and liver steatosis (S) using ROC curves. In the evaluation, we used descriptive statistics, correlation and regression analysis of the relationships between the occurrence of dg. fibrosis (F) and steatosis (S) and measured laboratory indicators. We used SPSS IBM ver. 18.

Table 1 shows a statistically significant correlation between the presence of liver fibrosis detected by Fibroscan and parameters of total, visceral fat and BMI (body mass index). Table 2 shows a statistically significant correlation between the presence of liver fibrosis and the so-called liver function tests: AST, ALT, ALP. The same correlation with AST, ALT and ALP was also confirmed at a statistically significant level for the liver steatosis parameters (results are shown in Table 3). A statistically significant correlation for the presence of liver fibrosis was not confirmed for the indicators of the fat spectrum (CHOL, TAG, HDL, LDL). A statistically significant correlation was not confirmed between the presence of liver steatosis detected by transient elastography and the parameters of total, visceral fat and BMI. We also created ROC curves for all the mentioned correlations.

**Table 1. Correlation of the presence of liver fibrosis and fat composition on the Tanita scale**

| Research file parameters | FIBROSIS | Total fat | Visceral fat | BMI |
|---|---|---|---|---|
| Pearson correl. coefficient | 1 | 0.220** | 0.212** | 0.377** |
| *p*-value | | 0.005 | 0.005 | 0.001 |
| Number | 170 | 170 | 170 | 166 |

* Correlation is significant at the 0,05 level (2-tailed); ** correlation is significant at the 0,01 level (2-tailed).

**Table 2. Correlation of the presence of liver fibrosis and the results of liver function tests**

| Parameters | Fibrosis | AST | ALT | GGT | ALP |
|---|---|---|---|---|---|
| Pearson correl. coefficient | 1 | 0.240** | 0.289** | 0.120 | 0.179* |
| *p*-value | | 0.003 | 0.001 | 0.136 | 0.025 |
| Number | 170 | 155 | 156 | 155 | 156 |

* Correlation is significant at the 0,05 level (2-tailed); ** correlation is significant at the 0,01 level (2-tailed).

**Table 3. Correlation of the presence of steatosis and the results of liver function tests**

| Parameters | Steatosis | AST | ALT | GGT | ALP |
|---|---|---|---|---|---|
| Pearson coefficient | 1 | 0.240** | 0.289** | 0.120 | 0.179* |
| *p*-value | | 0.003 | 0.001 | 0.136 | 0.025 |
| Number | 170 | 155 | 156 | 155 | 156 |

* Correlation is significant at the 0,05 level (2-tailed); ** correlation is significant at the 0,01 level (2-tailed).

We found 1 HBsAg positivity in our file – we suggested to the patient further diagnosis through our clinic. Antibodies against hepatitis C were negative in our group.

## Discussion

NAFLD, associated primarily with type 2 DM and metabolic syndrome, is thought to be the most common chronic disease worldwide, affecting 15–40% of the world's population [32].

Clinically, NAFLD can be manifested by fatigue, lethargy, daytime sleepiness, abdominal discomfort. Rarely, it is manifested by signs of hepatic insufficiency or portal hypertension (in case of liver cirrhosis). It is mostly clinically asymptomatic; an increased activity of aminotransferases or liver steatosis is accidentally detected during USG examination of the liver [33].

Liver transplants performed in Europe for liver cirrhosis and hepatocellular carcinoma associated with non-alcoholic steatohepatitis (NASH) increased from 0.2% to 1.2% (2014–2017) and in the USA NASH became the 2nd leading cause of liver transplants in 2015 and is expected to overtake it soon to the first place [34]. It is the factor forcing significant everyday lifestyle adjustments that impair quality of life among in rising number of patients [35] that need to be expected and thus clearly explained to them in advance, before they consent to the transplantation procedure [36], and properly documented, in the form demanded by law [37], by their physicians [38] including especially family doctors [39] as one of the most trusted sources of information [40].

In our group of patients, 66% were overweight and obese, 59% of the group had fatty liver. 20.5% of the participants of the event were diagnosed with liver fibrosis by accident! Therefore, general practitioners in the outpatient clinics should pay more attention to patients who are overweight and obese or have fatigue syndrome. The probability of liver damage increases with the simultaneous presence of DM2.

Transient elastography was adopted and standardized at the Annual European Congress of Hepatology in Copenhagen in 2009 and recommended by the EASL as a standard and safe method to determine the degree of fibrosis in selected liver diseases. This method is also recommended by the American (AASLD) and Asia-Pacific (APASL) associations for the study of liver diseases, as well as by the WHO.

Of course, the transient elastography device is not available everywhere, but we have the possibility to use non-invasive tests for indicative detection of fatty liver and liver fibrosis, such as FLI (fatty liver index) and FIB-4 score.

Among the non-invasive tests, the FLI test is suitable for large-scale screening, which is calculated using an online calculator from 4 input parameters (BMI, waist circumference, TAG and GGT). It is more convenient to use compared to ultrasonography. FLI < 30 excludes fibrosis, FLI ≥ 60 confirms fibrosis with 84% sensitivity and 97% specificity.

Fib-4 combines standard biochemical tests augmented by platelet count, serum ALT and AST activity, and patient age. Its calculation is as follows (it is also available on the Internet):

- Fib-4 = age ([years] x AST [U/L]) / ((PLT [10(9)/L]) x (ALT [U/L])(1/2)).
- FIB-4 scores < 0.6 almost 100% rule out significant fibrosis Metavir F2–F4.
- FIB-4 scores > 1 indicate a 62% probability of significant fibrosis Metavir F2–F4.
- FIB-4 scores < 1.45 indicate the Metavir F0–F2 stage with approximately 92% probability.
- FIB-4 scores > 3.25 indicate an 82% probability of advanced fibrosis (Metavir F3–F4).

In 2010 and 2014, World Health Assembly resolutions WHA63.18 and WHA67 recognized viral hepatitis as a global public health problem. It directed the WHO to develop and implement a comprehensive strategy for viral hepatitis, including the development of guidelines for member states on the diagnosis and treatment of HBV (hepatitis B) and HCV (hepatitis C) [41, 42].

In 2018, an immunological review was conducted in Slovakia. A total of 4,215 serum samples were examined for the presence of hepatitis C. A total of nine positive samples were detected, which were evaluated as reactive and were further subjected to a confirmatory laboratory examination. Four positive cases were confirmed by the Western Blot confirmatory test. The prevalence of positive cases in the examined set reached a value of 0.095%. After detection, the positive cases were immediately epidemiologically treated and were provided with appropriate health care [43].

In our research group, we did not detect even 1 case of hepatitis C in a general population.

However, in Slovakia, the incidence of CHC (chronic hepatitis C) is much higher in marginalized communities, where the simultaneous coincidence of several risk factors for the transmission of hepatitis C (intravenous drug use, tattoos, promiscuity) is common. Current viral hepatitis screening activities should be carried out in these communities.

## Conclusions

Although NAFLD is the most common liver disease, awareness of NAFLD is still relatively low and demand modern systemic education approach [44] similar to that applied in case of other civilisation diseases afflicting ageing societies [45]. For example, in a survey of adults with NAFLD, only 4.4% of them were aware that they suffered from liver disease. In a survey of hepatologists, gastroenterologists, endocrinologists, and primary care physicians, 47–67% of them believed that very few patients (< 10%) with fatty liver had symptoms, although 79–87% of them admitted that the quality of life of patients with NAFLD is impaired [46].

NAFLD provides a large field of action for interventions by general practitioners. In overweight and obese patients, NAFLD screening should be performed with a focus on measuring blood pressure, weighing the patient, measuring waist and hips circumference, determining the level of cholesterol, liver function tests, blood glucose levels and sending patients for an ultrasonographic examination of the abdominal cavity. These examinations can also be carried out during the patient's preventive examination, which is reimbursed by health insurance companies once every 2 years.

General practitioners are the first to come into contact with the patient and can help and provide useful advice on lifestyle changes. Only then does a specialist follow, who focuses more on the treatment of NAFLD comorbidities. In the management of liver diseases, the position of general practitioners is irreplaceable.

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Tables: 3
Figures: 3
References: 46

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