

# IMPORTANCE AND USE OF TRANSIENT ELASTOGRAPHY IN THE MANAGEMENT OF PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE

Význam a použitie tranzientnej elastografie v manažmente pacientov s nealkoholickou tukovou chorobou pečene

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## SÚHRN

**Úvod:** Nealkoholová tuková choroba pečene (NAFLD) je v súčasnosti klasifikovaná ako jedna z najvýznamnejších chronických ochorení pečene civilizácie. Nedávne epidemiologické štúdie potvrdili 30% celosvetovú prevalenciu nealkoholovej tukovej choroby pečene. NAFLD a jej progresívna forma nealkoholová steatohepatitída (NASH) sa objavujú čoraz častejšie a vyžadujú urgentné opatrenia.

**Cieľ:** Analýza komplexnej skupiny pacientov s nealkoholovou tukovou chorobou pečene/nealkoholovou steatohepatitídou, ktorí boli vyšetrení inovatívnou diagnostickou metódou tranzientnej elastografie (TELP) v období od januára 2015 do februára 2020 na hepatologickom oddelení Polikliniky SZU, na ktorom sa metóda zaviedla ako prvá na území Slovenskej republiky a strednej Európy v roku 2009.

**Metódy:** Do štúdie bolo zaradených 4 623 vyšetrených pacientov. U 1 048 pacientov bola potvrdená NAFLD/NASH, u 535 mužov a 513 žien vo veku od 18 do 96 rokov. Analyzovali sme obdobie od januára 2015 do februára 2020. Všetci pacienti boli vyšetrení novou metódou tranzientnej elastografie na kvantifikáciu fibrózy pečene na hepatologickom oddelení Polikliniky SZU. Na štatistické vyhodnotenie sme použili štatistický softvér IBM SPSS Statistics, Verzia 23.

**Výsledky:** Analýzou súboru sme zistili prítomnosť NAFLD u 203 pacientov a jej progresívnu formu NASH u 845 pacientov. Priemerný vek mužov bol 48,6 rokov ( $\pm$  13,3 štandardná odchýlka) a priemerný vek žien bol 57,1 rokov ( $\pm$  12,1 štandardná odchýlka).

**Záver:** Analýza komplexnej skupiny pacientov potvrdila vysoký výskyt NAFLD/NASH choroby v reálnej klinickej praxi a zvýšenú prítomnosť progresívnej formy NAFLD, resp. zvýšený výskyt F1-F4 fibrózy v kohorte NASH. Štúdia tiež potvrdila významný prínos metodiky TELP v diagnostike, perspektívnom monitorovaní a manažmente pacientov s NAFLD/NASH v klinickej praxi.

**Kľúčové slová:** nealkoholová tuková choroba pečene, tranzientná elastografia, nealkoholová steatohepatitída

## **SUMMARY**

**Introduction:** Presently, non-alcoholic fatty liver disease (NAFLD) is classified as one of the most significant chronic liver diseases of civilization. Recent epidemiological studies have confirmed a 30% worldwide prevalence of the non-alcoholic fatty liver disease. NAFLD and its progressive form, non-alcoholic steatohepatitis (NASH), are emerging more frequently and require urgent actions.

**Goal:** Analysis of the complex group of patients with non-alcoholic fatty liver disease/non-alcoholic steatohepatitis that were examined by the innovative diagnostic method transient elastography (TE) in the period from January 2015 to February 2020 on the hepatological department of SZU polyclinic on which the method was introduced first in the territory of the Slovak Republic and Central Europe in 2009.

**Methods:** The study included 4 623 examined patients. In 1 048 patients NAFLD/NASH was confirmed, consisting of 535 males and 513 females in the age ranging from 18 to 96 years. We analyzed the period from January 2015 to February 2020. All patients were examined by a novel method of transient elastography, for quantification of liver fibrosis on the hepatological department of SZU polyclinic. We used statistical software IBM SPSS Statistics, Version 23, for statistical evaluation.

**Results:** Analysis of the group of patients revealed the presence of NAFLD in 203 patients and its progressive form NASH in 845 patients. The average age of males was 48,6 years ( $\pm$ ) 13,3 standard deviation, and the female's average age was 57,1 years ( $\pm$ ) 12,1 standard deviation.

**Conclusion:** Analysis of the whole group of patients confirmed the high incidence of NAFLD/NASH disease in real clinical practice and increased presence of a progressive form of NAFLD, respectively, increased occurrence of F1-F4 fibrosis in the NASH cohort. The study also confirmed the significant contribution of TE methodology in diagnosis, prospective monitoring, and management of patients in clinical practice.

**Keywords:** non-alcoholic fatty liver disease, transient elastography, non-alcoholic steatohepatitis

## **Introduction**

Ludwig and co-workers first introduced the original representation of fatty liver disease in patients without significant alcohol consumption in 1980 (5). NAFLD/NASH disease is considered among the most critical priorities of today's world due to its increasing incidence, prevalence, and severity. The clinical course of the disease is principally divided into two primary phenotypes. Non-alcoholic steatosis also called a non-alcoholic fatty liver (NAFLD) disease accompanied by hepatic steatosis, is practically free from inflammation and fibrosis. The second subtype is non-alcoholic steatohepatitis (NASH) is considered as a progressive form of non-alcoholic fatty liver disease, characterized by the accumulation of fat in the liver cells, inflammation, and fibrogenesis which can progress to liver cirrhosis and its complications in some individuals. The dreaded and most severe complication is the development of hepatocellular carcinoma (HCC) (1-2, 8).

Novel non-invasive dynamic diagnostic strategies were developed over the past decade, for determining the diagnosis of fibrosis and specifying its degree. Transient elastography has received considerable attention in clinical practice for its non-invasive, rapid assessment of existing liver fibrosis based on the measurement of hepatic stiffness in patients with chronic hepatic disease. The advantages of transient elastography are its flexibility, financial frugality, easy reproducibility, and excellent patient's acceptance (3, 7).

## **Material and methods**

Investigated group of the patient (1 048) were chosen from all patients (4 623) who undergone transient elastographic examination in a specific time interval from January 2015 to February 2020 on the hepatological department of SZU policlinic in Bratislava. From all patients who have undergone this type of examination were selected only those in which NAFLD/NASH disease was confirmed. Subsequently, we processed the results and data including gender, age, liver stiffness, interquartile range (IQR), degree of fibrosis, year of examination, and diagnosis of each patient from performed TE examination.

The TE examination was performed in a patient lying supine on the bed with the right arm in maximal abduction, with the ultrasound-like probe placed on the skin over the liver in the patient's right mid-axillary line. TE technology works on the principle of measuring shear wave velocity. TE consists of an ultrasound transducer on the end of the vibrator which is positioned over the liver in the intercostal space, and which produces vibration of a mild amplitude and frequency of 50-MHz, consequently inducing an elastic shear wave that propagates through the liver. As the wave is passing inside the liver, the transducer located on the end of the probe measures the velocity of the shear wave in standard unit meters per second.

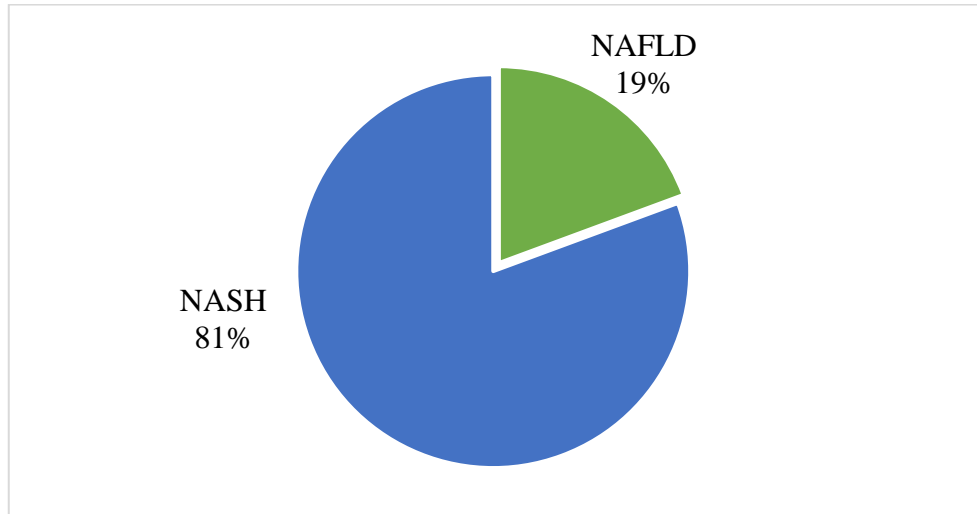
The shear wave velocity is then converted into liver stiffness. The result of the examination is the value of the elasticity of the liver parenchyma in kilopascals (kPa) (3-4, 6-7).

## Results and Discussion

The study included 4 623 examined patients. In 1048 patients NAFLD/NASH was confirmed, consisting of 535 males and 513 females in the age ranging from 18 to 96 years. Figure 1. demonstrates the ratio between NAFLD/NASH in examined patients. The progressive form NASH was confirmed in the majority of patients which indicates late capture of the disease; the patients had already been in the active progressive stage of the disease. It is necessary to highlight the importance of regular prevention and early capture of the disease by which we may avoid the progressive and active stage of the disease which may lead to liver cirrhosis and in the worst scenario to HCC.

**Figure 1. Percental ratio of NAFLD / NASH in the total number of examined patients in interval from January 2015 to February 2020.**

**Obrázok 1. Percentuálny pomer NAFLD / NASH v celkovom počte vyšetrených pacientov v intervale od januára 2015 do februára 2020.**



**Table 1. Degrees of fibrosis in patients with diagnosed NAFLD****Tabuľka 1. Stupne fibrózy u pacientov s diagnostikovanou NAFLD**

Degree of fibrosis	Male	Female
F0	74	98
F0-F1	1	0
F1	4	12
F2	2	4
F2-F3	6	2

**Table 2. Degrees of fibrosis in patients with diagnosed progressive form of NASH steatohepatitis in period of 2015-2020****Tabuľka 2. Stupne fibrózy u pacientov s diagnostikovanou progresívnou formou NASH v období rokov 2015 - 2020**

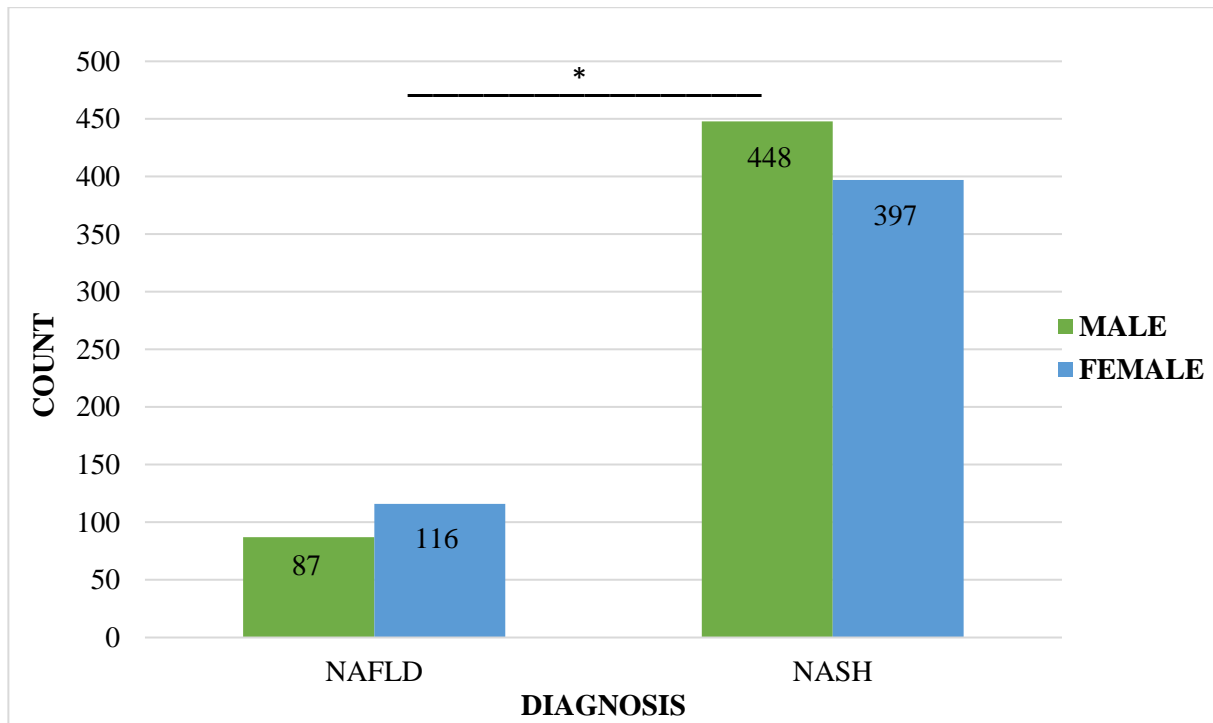
Degree of fibrosis	Male	Female
F0	319	258
F0-F1	3	0
F1	37	24
F1-F2	2	1
F2	30	38
F2-F3	11	13
F3	16	14
F3-F4	11	11
F4	19	38
Total	448	397

Findings in the group of patients with NASH (Table 2) shown that in 359 males and 282 females were detected stages F0, F0-F1, F1 which confirm the chronic duration of fibrosis. Significant

fibrosis was proven in 32 males and 39 females. The progressive fibrosis was detected in 27 males and 27 female patients. Thirty males and 49 females were in stage F3 - F4 that constitutes the stage of developed cirrhotic fibrosis.

**Figure 2. Ratio of males and females with NAFLD/NASH disease**

**Obrázok 2. Pomer mužov a žien s NAFLD/NASH ochorením**



\* $p < 0,05$

NAFLD is affecting statistically significantly ( $p < 0.05$ ) more females than males. However, fewer females had the progressive form NASH compared to males as visible in figure 2.

**Table 3. Prevalence in the analyzed period from January 2015 to February 2020**

**Tabuľka 3. Prevalencia v analyzovanom období od januára 2015 do februára 2020**

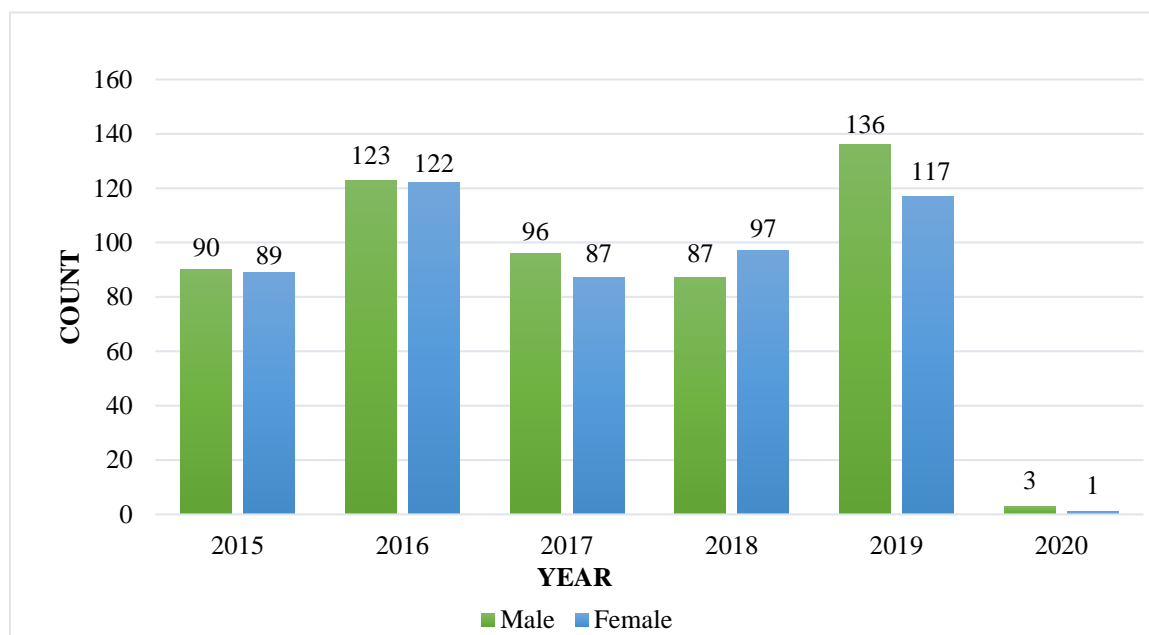
Year	Number of patients with NAFLD/NASH
2015	179 (23%)
2016	245 (26%)
2017	183 (19,3%)
2018	184 (22%)

2019	253 (23%)
2020	4

In the years 2015 and 2016 increased growth of patients with NAFLD/NASH was observed, however, the number of patients in the year 2017 was lower compared to the years 2015/2016. The increasing tendency was again observed in 2018/2019. In 2020 only patients examined in January and February are counted which the number 4 explains.

**Figure 3. Prevalence in males and females with NAFLD/NASH disease in period from January 2015 to February 2020**

**Obrázok 3. Prevalencia mužov a žien s ochorením NAFLD/NASH v období od januára 2015 do februára 2020**



**Table 4. Number of patients examined more than once by TE method in period from January 2015 to February 2020**

**Tabuľka 4. Počet pacientov vyšetrených viac ako jedenkrát metódou TELP v období od januára 2015 do februára 2020**

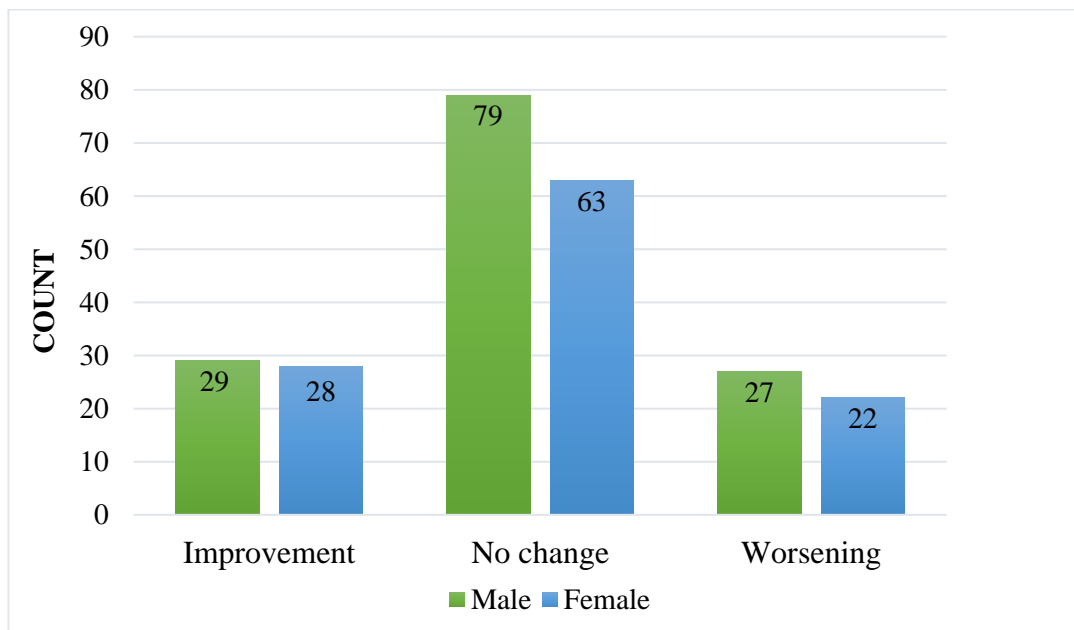
Gender	NAFLD	NASH
Male	8	127
Female	4	109
Total	12	236

The total number of all patients who have undergone TE examination more than once was 248 from all 1048 investigated patients. The main reason for repeated examination was the management and monitoring of the stage of the disease.

Because the TE examination is a non-invasive and painless method, it does not only serve as the diagnostic method for assessment of hepatic fibrosis. Serial measurements may be performed in the outpatient clinic with the immediate result to monitor disease progression, the effectiveness of the therapy and predicting the development of liver-related complications (3).

**Figure 4. Results of monitoring in patients with NAFLD/NASH who undergone TE examination more than once**

**Obrázok 4. Výsledky monitorovania u pacientov s NAFLD / NASH, ktorí podstúpili vyšetrenie TELP viac ako jedenkrát**



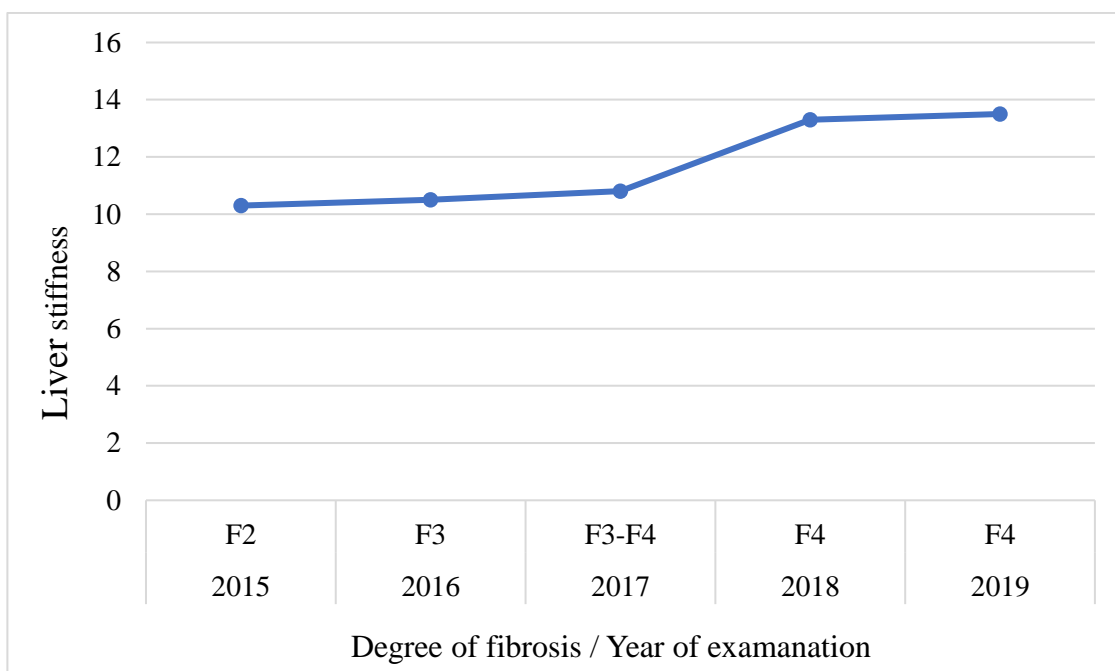


Improved liver fibrosis stage was proven in 29 males and 28 females. In seventy-nine males and 63 females wasn't observed any change. Worsening of liver fibrosis occurred in 27 males and 22 females.

The importance of prospective utilization of transient elastography in patient management with NAFLD/NASH is documented in two case reports. The first case report presents a deterioration, respectively, a progression of liver fibrosis in patient who did not respect the recommendation of complex management of the disease. The second case shows improvement and reduction of liver fibrosis in the patient who was rationally managed and treated. A more detailed analysis of these case reports was not the aim of this publication, and we plan to publish it in the next work.

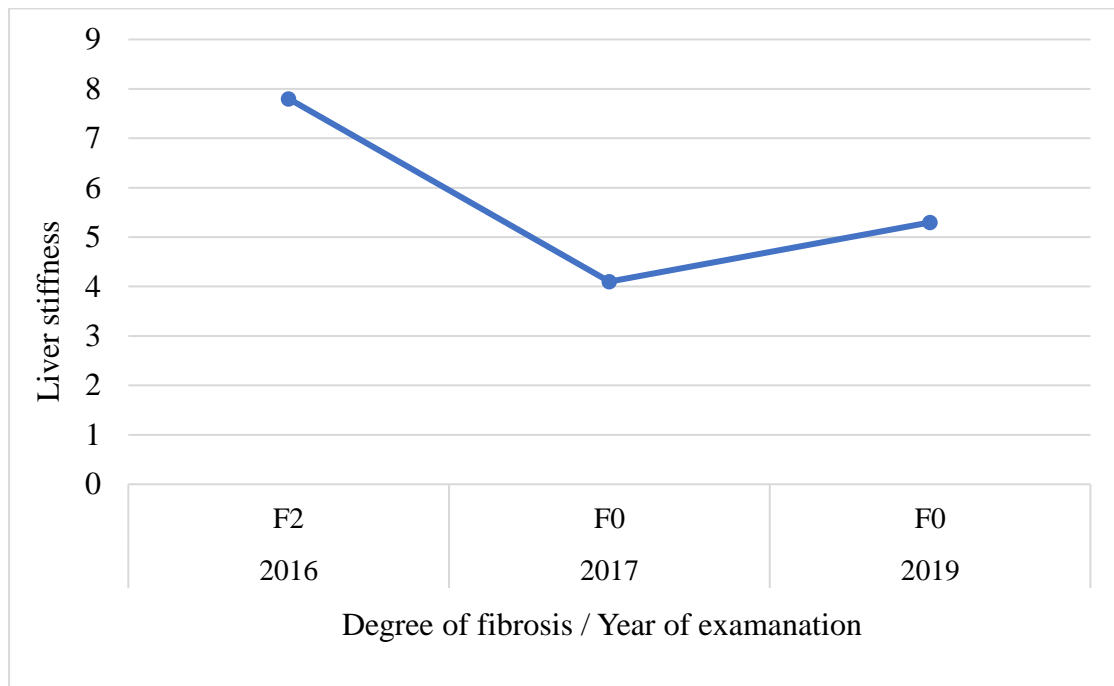
**Figure 5. Deterioration of liver fibrosis in patient with progressive form of NASH**

**Obrázok 5. Zhoršenie fibrózy pečene u pacienta s progresívnou formou NASH**



**Figure 6. Regression of liver fibrosis in patient with progressive form of NASH**

**Obrázok 6. Regresia fibrózy pečene u pacienta s progresívnou formou NASH**



### Conclusion

Transient elastography as a non-invasive, rapid, safe and effective method has a significant asset in diagnosis, surveillance, and management of patients with NAFLD/NASH disease. Analysis of patients confirmed the high occurrence of NAFLD/NASH disease, notably increased appearance of the stage of F1-4 fibrosis in NASH cohort and also affirmed the growing incidence of NAFLD/NASH in period 2015-2020 in real clinical practice.

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