Bulletin of the *Transilvania* University of Braşov
Series VI: Medical Sciences • Vol. 7 (56) No. 2 - 2014

THE VALUE OF ULTRASOUND CRITERIA IN SCREENING DIAGNOSIS FOR NON ALCOHOLIC FATTY LIVER DISEASE

T. NEDELOIU[1] M. RADOI[1] I. MUNTEAN[1]
O. POPA[2] C. IDOMIR[2]

Abstract: *Common method of screening diagnostic of NAFLD remained abdominal ultrasound, despite his modest sensitivity and specificity. Clinician decision depends radiologist to diagnose and staging this disease. We have analyzed the most five used ultrasound criteria and liver lobes diameters from 132 patients with NAFLD. Purpose of this study was to rank the weight of these criteria at diagnosis, to assess the degree of subjectivity in diagnosis and simplify diagnosis by grouping criteria in only two factors in aim to decrease interobserver variability.*

Key words : *fatty liver disease, steatosis, ultrasounds criteria, diagnosis.*

1. Introduction

Hepatic steatosis, „fatty liver" or „liver fat accumulation", especially through its non-alcoholic component, is the most frequent cause of the chronic liver disease around the world [1], [2], [3]. Non-alcoholic fatty liver disease (NAFLD) is charac-terised by the accumulation of fat, predominantly triglycerides, in the hepatocytes of the persons who do not drink or who drink only little alcohol (less than 10-40 gr/day) [6]. Non-alcoholic fatty liver includes a wide range of hepatic lesions, from simple steatosis to steatohe-patitis (NASH = non-alcoholic steatohe-patitis). The symptomatic expression is minimal, hepatic steatosis being most frequently asymptomatic, but with an evolutive potential towards cirrhosis and hepatocellular carcinoma [5]. Recent data have presented the increasing need for hepatic transplant in NAFLD patients [10, 16].

The increased prevalence of NAFLD, the long asymptomatic evolution and the possible complications have led to the reconsideration of the „fatty liver" from a mere epiphenomenon of the metabolic syndrome to a global public health problem [13].

NAFLD's „gold standard" diagnosis is the hepatic biopsy. The invasive character of hepatic biopsy determined the increase of the weight of non-invasive methods that include biochemical tests and different imaging methods differentiated through their degree of sensitivity and the diagnostic specificity of NAFLD. In the meta-analysis of 2011, the use of hepatic biopsy as a reference test in the diagnosis of NAFLD assessed a sensitivity of 73-90% for the liver ultrasonography, 46-72% for the CT-scan, 82-97% for the magnetic

[1] Faculty of Medicine, *Transilvania* University of Braşov.
[2] Braşov County Clinical Emergency Hospital.

resonance imaging (MRI) and 82-88% for the proton magnetic resonance spectroscopy (MRS), the specificity of these method being 69-85% for the ultrasound examination, 88-94% for the CT-scan, 76-95% for the MRI and 92-95% for the MRS [4].

Simple hepatic ultrasonography prevailed in the „diagnostic screening" of the „fatty liver" owing to the accessibility of the method, even though sensitivity is low in the diagnosis of moderate fat accumulation (20%-30% fat of the total body weight) and of the focal hepatic steatosis [15, 12]. Dasharty's sonographic criteria according to which the diagnosis of hepatic steatosis is formulated are: 1) „Increased hepatic brightness" defined as a homogenously increased echogenicity or hyperechogenicity (He), 2) Posterior attenuation of the right lobe (RLpA), 3) The increased contrast between the right kidney and the liver (HRC), 4) The loss of visualisation of the right diaphragm (LVRD) and 5) The diminished visibility of the intrahepatic vessels (DVIV) [8]. It is a known fact that the sonographic criteria of the diagnosis of fatty liver facilitate the inter-observer subjectivism and reduce the sensitivity and specificity of the method [14]. For these reasons, in the diagnosis of fatty liver, the simple liver ultrasound is usually completed by biochemical investigations (α-2 macro-globulin, haptoglobin, apolipoprotein A-1, γ-glutamyl transpeptidase, total bilirubin, alanine-aminotransferase, basal glycaemia, cholesterol, triglycerides, thrombocytes etc.) that allow the calculation of diagnostic scores such as the SteatoTest, FibroMeter, Fib4, with the determination of cytokeratin-18 or with hepatic elastography [11].

2. Purpose of the study

The main objectives of the study were the assessment of the relationship between the diagnosed fatty liver through the use of the „five sonographic criteria" and the hepatomegaly assessed through the diameters of the hepatic lobes, the determining of the weight of each sonographic criterion in the formulation of the diagnosis of fatty liver disease and the severity of this disease by using a score of the intensity of the hepatic sonographic modifications.

The secondary objectives included the identification of some criteria that should simplify the diagnosis and should increase the level of trust in the sonographic diagnosis of the fatty liver disease.

3. Material and Methods

This is a prospective assessment study of the weight of the sonographic criteria on which relies the fatty liver diagnosis formulated by 9 radiologists with competence and experience of over 10 years in the abdominal ultrasound exam. The ultrasound exam was performed on 132 patients and it was recorded in the „Assessment chart" on which the 5 criteria of diagnosis of the fatty liver disease recommended by Dasharty [8] had been pre-printed, to which the diameters of two hepatic lobes were added. In line with each criterion there are three degrees of modification, one of which the operator needs to choose by checking. Based on the sonographic criteria, the physician who performed the ultrasound set the diagnosis of „fatty liver", the level of trust in the formulated diagnosis being appreciated by checking the final diagnosis as „possible, probable or certain steatosis" (Fig. 1).

A sample „Assessment chart" of a patient with a total score (ToSc) of 9 points and „probable" steatosis can be found in Fig. 1.

Please check or mark with 1 to 3 points the presence of the following signs of hepatic steatosis, then check one of the options of your subjective impression of the trust in the diagnosis.

Right lobe diameter = 147 mm / Left lobe diameter = 85 mm			
	1	**2**	**3**
Hyperechogenicity		**X**	
Posterior attenuation of the right lobe			**X**
The increased contrast between the right kidney and the liver	**X**		
The loss of visualisation of the right diaphragm	**X**		
The diminished visibility of the intrahepatic vessels		**X**	

Your subjective impression of the trust of the diagnosis		
	possible steatosis	
	probable steatosis	**X**
	certain steatosis	

Fig. 1. *A sample „Assessment chart" of a patient with a total score (ToSc) of 9 points and „probable" steatosis*

132 sonographic „assessment charts were recorded with the diagnosis of fatty liver. Demographic data were recorded for the assessed patients: age, gender, body weight, body mass index, and the diseases that might be related to the fatty liver disease (diabetes mellitus, metabolic syndrome, obesity and chronic hepatitis). The demographic data and those referring to the diagnosis were not mentioned in the sonographic „assessment chart" in the attempt to decrease subjectivity in the formulation of the final diagnosis and the inter-observer variability.

The intensity of the modification of the sonographic criteria was graded from 1 to 3 (Tab. 1).

Table 1

The score of the degrees of modification of the sonographic diagnosis criteria of the fatty liver

	Degrees of modification		
	1	**2**	**3**
Hyperechogenicity (He)	mild enhance	intermediate	accentuated
Posterior attenuation of the right lobe (RLpA)	mild attenuation	intermediate	accentuated
The increased contrast between the right kidney and the liver (HRC)	mild enhance	intermediate	accentuated
The loss of visualisation of the right diaphragm (LVRD)	very good	good	faded
The diminished visibility of the intrahepatic vessels (DVIV)	mild enhance	intermediate	accentuated

A total score (ToSc) obtained through the summing up of the points given to each diagnostic criterion was calculated. The theoretical minimum ToSc is 5 (1 point for each diagnostic criterion), whereas the maximum score is 15 (3 points for each diagnostic criterion):

The sonographic severity of the fatty liver has been assessed based on the value of the ToSc obtained by each patient and it was recorded as stage 1 steatosis (5-8 points), stage 2 (9-11 points) and stage 3 (12-15 points).

The weight of each criterion in the formulation of the fatty liver diagnosis was calculated as follows: the ToSc of all the patients was summed up and, out of this sum, the weight of each sonographic criterion summed up for all the patients was calculated proportionally.

The patients with focal fatty liver and those with renal diseases that might have influenced the „sonographic hepatorenal contrast" (HRC) criterion were excluded from the assessment.

Antecedent infections with the hepatitis B or C virus and alcohol consumption habits of more than 40mg/day were considered possible causes of the steatosis. In the absence of antecedent infections with the hepatitis B or C virus and of the abuse of alcohol, the fatty liver disease was considered „non-alcoholic".

Statistic analysis

The supposition of normality of the data was confirmed using the KS and SW tests. Confidence intervals of 95% were calculated for averages using „one sample" T-test. The comparison of the average hepatic diameters was done using the simple ANOVA analysis with the Levene test of assessment of the homogeneity of variance. The frequency of the sonographic criteria by severity degrees in the contingency table were subjected to the $\chi 2$ test. Parametric correlations (Pearson correlations, r) were used between the diameters of the lobes, and non-parametric correlations were used between the diameters and the total score (Spearman'rho correlations, rs), and the R2 determination coefficient was calculated for r and rs. The „exploratory factor analysis", the „principal axis factoring" method was used for normally distributed data, with the „varimax" orthogonal rotation, in the extraction of the most important latent factors from the matrix of the degrees of modification of the sonographic criteria and the simplification of the diagnosis. The choice of the number of factors was done through a „parallel analysis" based on the value of the „engenvalue" index, over 1. For justification of the use of the factor analysis, the value of the KMO index and the level of significance of Bartlett's test of sphericity were used.

4. Results and Discussion

The study has included 132 patients, which were diagnosed with fatty liver disease. The average age of the patients was of 57.9 years [C.I. 95% = 56-59.7]; there were 68 male patients (51.4%) and 64 female patients (48.6%). The aetiology of the steatosis was non-alcoholic for 104 patients (78.8%), for another 3 patients (2.3%) it was associated with viral chronic hepatitis and for 25 patients (18.9%) it was ethanolic.

The total score (ToSc) for the 132 patients was of 1175 points. This total consisted of a contribution of: 296 points (25.2%) from He, 270 points (23%) from RLpA, 226 points (19.2%) from HRC, 197 points (16.8%) from LVRD and 186 points (15.8%) from DVIV.

The assessment of the weight of the ultrasound criteria in determining the diagnostic of fatty liver shows that each criterion has a different contribution to the ToSc and that the weight of the contribution has a tendency to decrease from He to RLpA and with similar values to HRC, LRVD and finally to DVIV. (Fig. 2)

Table 1

The average of the anterior diameters of the hepatic lobes based on the aetiology of the fatty liver

	Etiology	Number	Diameters mean (mm) [95%C.I.]	F	p
Right Lobe	non-alcoholic	104	156 [152-160]	0,999	0,371
	alcoholic	25	159 [149-168]		
	viral	3	172 [90-254]		
Left Lobe	non-alcoholic	104	73 [71-76]	1,347	0,264
	alcoholic	25	73 [68-78]		
	viral	3	85 [53-117]		

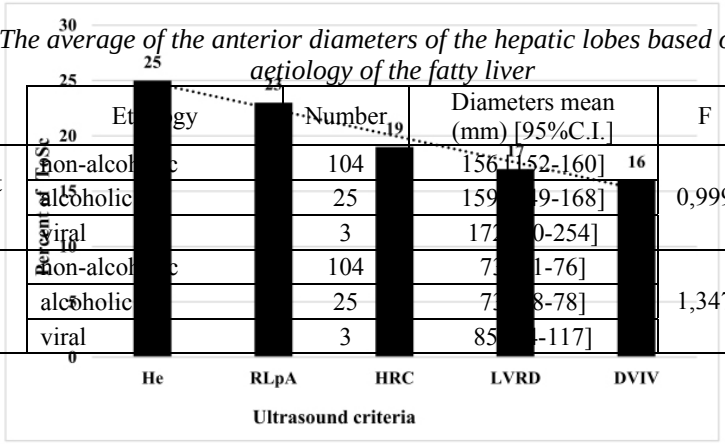

Fig. 2. *The decreasing weight of the ultrasound criteria in determining the diagnostic of fatty liver with the line that shows this tendency.*

The severity of the steatosis was determined by calculating the total score of the intensity of the modifications in the ultrasound criteria of diagnostic, which showed a ToSc between 5 and 8 points and a stage 1 steatosis in 64 patients (48.5%), a ToSc between 9 and 11 points and a stage 2 steatosis in 47 patients (35.5%), a ToSc between 12 and 15 points and a stage 3 steatosis in 21 patients (16%).

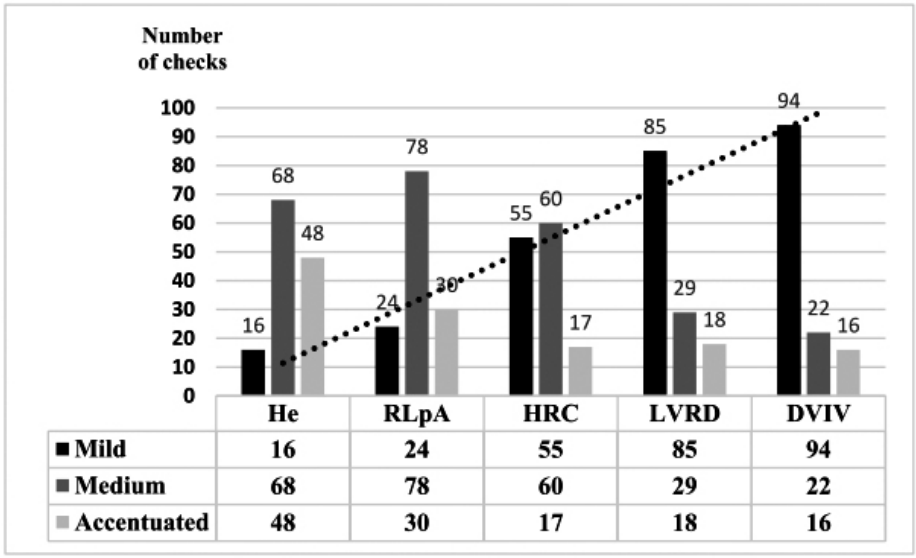

Fig. 3. *The assessment frequency of the modification degrees of the sonographic diagnosis criteria of the fatty liver*

The analysis, in a contingency table, of the three degrees of modification of the intensity of the sonographic criteria shows significant differences between their frequencies (the $\chi 2$ test with $p < 0.001$ for each criterion). This analysis also determines that for He the predominant modifications are „average and accentuated", whereas for LVRD and DVIV, the predominant modification is „slight". (Fig. 3) We would have expected the frequency of the degrees of modification of the intensity of the ultrasound criteria to be approximately the same. The dotted line represents the increasing tendency for „slight" changes.

Since fatty liver is often accompanied by hepatomegaly, I have studied the potential influence of the sizes of the hepatic lobes upon the frequency and intensity with which the modifications of the five sonographic diagnosis criteria were noted, the fact being known that the increased size and weight of the right lobe leads to a loss of visualisation of the right diaphragm (LVRD) and of the intrahepatic vessels (DVIV). [7]

The average value of the anterior diameter of the right lobe of liver (RLL) was of 157 mm [C.I. 95% = 153-160; min. = 108mm, max. = 221mm], whereas the average value of the anterior diameter of the left lobe (LLL) was of 73.5 mm [C.I. 95% = 71-75mm; min. = 42mm, max. = 118mm]. The average values of both the diameters were significantly ($p < 0.001$) higher than the normal values of the anterior diameters of the hepatic lobes (RLL 7cm in women and 10.5cm in men [9]), which reconfirms the association between steatosis and hepatomegaly. There is a significant positive correlation (Pearson's coefficient) between the diameters of the two lobes ($r=0.31$; $p<0.0001$), but the power of the correlation is smaller (the determining coefficient $R2 = 0.096$), which means that only about 10% of the size of the left lobe is directly correlated to the concurrent size of the right lobe. However, this was an unexpected fact for a disease that has a pathogenic mechanism that involves the liver as a whole.

The comparison of the average values of the anterior diameters of the two hepatic lobes (the simple ANOVA method) did not reveal any statistically significant difference of the RLL ($F2df = 0.999$; $p = 0.371$) and LLL ($F2df = 1.347$; $p = 0.264$) in relation to the aetiology of the fatty liver (Tab. 2).

The value of the total score (ToSc) of the intensity of modification of the sonographic diagnostic criteria of the fatty liver did not correlate significantly (Spearman' rho coefficient) with the size of the hepatic lobes. For the right lobe $rs = 0.02$; $p = 0.82$, whereas for the left lobe $rs = 0.170$; $p = 0.051$.

The stages of severity of the fatty accumulation (1, 2, and 3) did not correlate with the diameters of the hepatic lobes (RLL $rs = 0.05$; $p = 0.96$; LLL $rs = 0.14$; $p = 0.11$).

The physician's final subjective formulation of the diagnosis has shown that fatty liver has been considered „certain" in 107 patients (81%), „probable" in 19 patients (14.4%) and „possible" in 6 patients (4.5%). The ANOVA analysis did not reveal any significant differences between the level of the diagnostic impression of the steatosis assessed as „certain", „probable" or „possible" and the sizes of the anterior diameters of the two hepatic lobes, even though there is an increasing tendency of the steatosis as „certain" in the patients whose anterior diameter of the right lobe was 158 mm and that of the left lobe was 75 mm (Fig.4). In other words, the size of the liver, assessed by measuring the lobe diameters, does not consistently influence the subjective impression in formulating the fatty liver diagnosis.

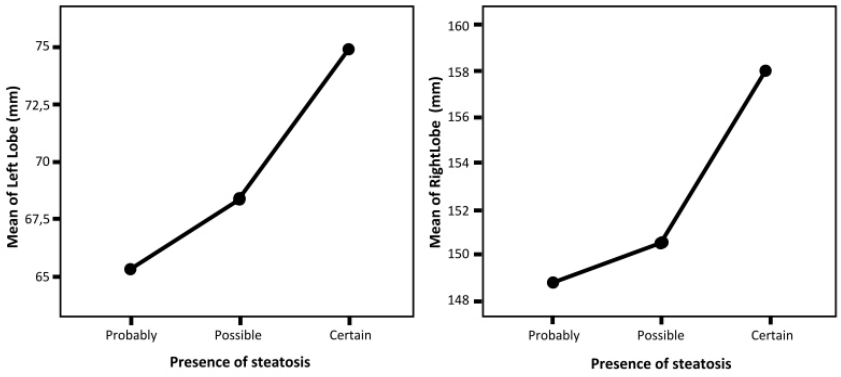

Fig. 4. *Relationship between the subjective diagnosis of fatty liver and the average values of the anterior diameter of the hepatic lobes*

From the data collected so far, it results that the value of the „five sonographic criteria" and the physician's subjective impression interfere differently in the diagnosis of fatty liver. Some of the sonographic criteria seem to be more valuable, whereas others seem to matter less in the formulation of the diagnosis. The question is whether come criteria may be relinquished, without any impact upon the diagnosis, or whether certain criteria may be grouped under a common name with a greater predictive power than that of each separate criterion. That is why, the importance concomitantly noting down the modifications of the „five sonographic criteria" and of the subjective impression that assesses the confidence in the diagnosis of fatty liver has been analysed through a method that is frequently used in psychology researches: „factor analysis". Factor analysis has also been applied because the weight of the sonographic criteria of diagnosis of the fatty liver and the frequency of the degrees of modification of these criteria was not evenly distributed. (Fig. 2 and Fig. 3)

Factor analysis was preceded by two different stages. The first stage consisted of subjecting the data to some suggestive tests for the existence of one or several common latent factors that would justify the use of the „factor reduction procedure". In this study, the latent factor is in fact a

group of several sonographic criteria of diagnosis with a greater predictive power than that of each separate criterion. The second stage consists of the „parallel analysis" aimed at identifying the optimal number of latent factors that have a diagnostic value (out of the 6 proposed by the statistical software).

The data resulted from the sonographic bulletins of the 132 patients, all tested for the KMO index (0.76) and the level of significance of Bartlett's test of sphericity (400.43; sig. < 0.0001), make factor analysis adequate.

In the second stage, the results of the „parallel analysis" render to latent factors evident (with „eigenvalue" > 1) for the sonographic criteria (Fig. 5)

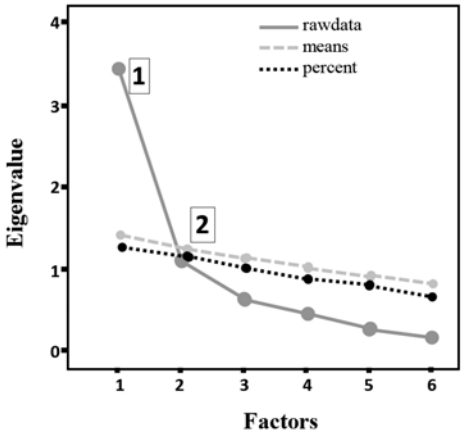

Fig. 5. *The „parallel analysis" suggests the existence of two common latent factors*

Latent Factor 2 that groups the criteria RLpA, He and the „subjective appreciation" was called „major association" in the diagnosis of the fatty liver, whereas Latent Factor 1 that groups the criteria LVRD and DVIV was called „minor association" of diagnosis (Tab. 3). We notice that HRC was not included in any of the latent factors owing to the fact that its correlation resembles both factors.

The results of the analysis show that the „major and minor association" contribute to the formulation of the diagnosis of fatty liver by 65.3% (the minor association by 33.3% and the major association by 32%).

The „major association" represents the first intention of the diagnosis supposition, and the „minor association" subsequently confirms the diagnosis. It coincides with the diagnostic practice in which the operator of the ultrasonography makes a first subjective impression of the diagnosis of fatty liver based on the hepatic brightness and possibly on the posterior attenuation, the hepatic diameters and the other diagnosis criteria being assessed only at a later stage.

The physician's share of subjectivity in the formulation of the diagnosis is about 34.7% (the remaining share out of 100% of the sum of the percentages of the „Major and Minor Association"), which reveals the inter-observer variability.

Table 2

Levels of saturation of the sonographic criteria

Rotated Factor Matrix[a]

	Factor	
	1	2
LVRD	**,980**	,199
DVIV	**,753**	,261
HRC	,522	,505
RLpA	,303	**,908**
He	,315	**,728**
Subjective impression	,079	**,451**

Extraction Method: Maximum Likelihood.
Rotation Method: Varimax with Kaiser Normalization.
a. Rotation converged in 3 iterations.

4. Conclusions

1. The weight of the sonographic criteria in the formulation of the diagnosis of fatty liver includes, in descending order, hepatic hyperechogenicity, posterior attenuation in the right hepatic lobe, diminishing of the hepatorenal contrast, loss of visualization of the right diaphragm and of the intrahepatic vessels.

2. The size of the liver assessed by measuring the lobe diameters does not consistently influence the subjective impression in the formulation of the diagnosis of fatty liver

3. In the ultrasound assessment there is a significant inter-observer variability that determines a high degree of subjectivity in the diagnosis and staging of fatty liver.

4. The subjective impression on the presence of steatosis shapes up during the first moments of the hepatic sonographic investigation and it is formed before measuring the diameters of the hepatic lobes, as it is based on the association of the hepatic hyperechogenicity with the posterior attenuation in the right hepatic lobe. Diagnostic certainty usually appears after the appreciation of the loss of visualisation of the right diaphragm and of the intrahepatic vessels.

Acknowledgments

Radiology Departament of County Clinical Hospital Emergency Brasov: Maria Carstea, Doina Leonte, Mariana Biris, Ileana Muntean, Rosana Manea, Andrei Deak, Mihaela Cioroiu, Cristina Dragomir, Claudia Gavris, Iulia Pintoiu

References

1. Angulo, P.: *GI epidemiology: nonal-coholic fatty liver disease.* In: Aliment Pharmacol Ther. 2007 Apr 15;25(8):883–889.
2. Angulo, P.: *Nonalcoholic fatty liver disease.* In: N Engl J Med. 2002 Apr 18;346(16):1221–1231.
3. Argo, C.K., Caldwell, S.H.: *Epidemiology and natural history of non-alcoholic steatohepatitis.* In: Clin Liver Dis. 2009 Nov;13(4):511–531.
4. Bohte, A., Werven, J., Bipat, S. et al.: *The diagnostic accuracy of US, CT, MRI and 1H-MRS for the evaluation of hepatic steatosis compared with liver biopsy: a meta-analysis.* In: European Radiology 2011;21(1): 87-97. doi 10.1007/s00330-010-1905-5.
5. Bugianesi, E., Leone, N., Vanni, E. et al.: *Expanding the natural history of nonalcoholic steato-hepatitis: from cryptogenic cirr-hosis to hepatocellular carcinoma.* In: Gastroenterology 2002 Jul;123(1):134-40. PubMed PMID: 12105842.
6. Chalasani, N., Younossi, Z., Lavine, J.E. et al.: *The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association.* In: Hepatology. 2012;55:2005–2023.
7. Chan, V., Perlas, A., S.N. Narouze (ed.), *Atlas of Ultrasound-Guided Procedures in Interventional Pain Management,* doi 10.1007/978-1-4419-1681-5_2, Springer, 2011.
8. Dasarathy, S., Dasarathy, J., Khiyami, A. et al.: *Validity of real time ultrasound in the diagnosis of hepatic steatosis: a prospective study.* In: J Hepatol. 2009; 51:1061–1067.
9. Douglas, C., Wolf.: *Clinical Methods: The History, Physical, and Laboratory Examinations*. In: *Evaluation of the Size, Shape, and Consistency of the Liver,* Chapter 94, 3rd edition. Boston. Butterworths, 1990.

10. Feldstein, A.E., Charatcharoen-witthaya, P., Treeprasertsuk, S. et al.: *The natural history of non-alcoholic fatty liver disease in children: a follow-up study for up to 20 years.* In: Gut. 2009 Nov; 58(11): 1538–1544.
11. Festi, D., Schiumerini, R., Marzi, L. et al.: *Review article: the diagnosis of non-alcoholic fatty liver disease – availability and accuracy of non-invasive methods.* In: Aliment Pharmacol Ther. 2013 Feb; 37(4): 392-400.
12. Hernaez, R., Lazo, M., Bonekamp, S. et al.: *Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a meta-analysis.* In: Hepatology. 2011;54: 1082–1090.
13. Roland, V.: *Non-alcoholic fatty liver disease: a non-problem or public health catastrophe?* In: Frontline Gastro 2010;1:3 147-148.
14. Saadeh, S., Younossi, Z.M., Remer, E,M. et al.: *The utility of radiological imaging in nonalcoholic fatty liver disease.* In: Gastroenterology. 2002;123: 745–750.
15. Shruti, H.M., Bryan, L., Nezam, H.A. et al.: *Exceeding the limits of liver histology markers.* In: Journal of Hepatology. Volume 50, Issue 1, Pages 1-3 (January 2009)
16. Starley, B.Q., Calcagno, C.J., Harrison, S.A.: *Nonalcoholic fatty liver disease and hepatocellular carcinoma: a weighty connection.* In: Hepatology. 2010 May; 51(5): 1820–1832.