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# THE ROLE OF ULTRASOUND EVALUATION IN THE DIAGNOSIS OF FATTY LIVER – IS AN ACCURATE STAGING POSSIBLE?

**Lazăr I. M.[1,2], Stefan M.[3], Aramă Victoria[1,2], Ion Daniela Adriana[2]**

[1.] *National Institute for Infectious Diseases Prof. Dr. Matei Bals*
[2.] *University of Medicine and Pharmacy Carol Davila*
[3.] *Polytechnic University of Bucharest*

**Abstract.** This paper presents the results from a research study which examines the correlations between the biological and morphopathological evaluation of the fatty liver and the ultrasound investigation. The purpose is to establish the utility and accuracy of ultrasound evaluation of fatty liver and to suggest an ultrasound staging of hepatic steatosis. Material and method: we evaluated 2 groups of patients – group A: 222 patients examined using ultrasound and liver biopsy and group B: 167 patients examined using ultrasound and steatotest. The obtained results demonstrate that the echographic evaluation is a reliable diagnostic method for liver steatosis, with over 0,82 sensitivity and over 0,90 specificity, depending on the steatosis stage.
**Keywords:** steatosis staging, fatty liver

## Introduction

Steatosis is the most common liver disease and affects approximately 20% of the general population, having the highest prevalence in the Caucasian race [1,2,3].

This affection may be associated with viral infections, alcohol intake, metabolic disorders or abnormal alimentary habits (NASH has been detected in over 80% of patients who are obese and in 1.2-9% of patients undergoing routine liver biopsy). The hepatic steatosis may progress to liver fibrosis and cirrhosis - 5-20% of patients with NASH develop cryptogenic cirrhosis (the so called burnt-out NASH) [4,5] and can also be associated with a lower viral response rate in case of interferon-based therapies. [6] The importance in diagnosing liver steatosis goes even further – a few authors emphasizing that a relation between the occurrence of HCC and the liver steatosis may exist. [8,9,10]

Noninvasive studies (CT, MRI, US) may identify the presence of a fatty liver, but without distinguishing between benign steatosis and steatohepatitis. Therefore liver biopsy and histopathological examination are required for an accurate assessment and grading of steatosis, representig at the moment the goldstandard for liver steatosis staging.

Diagnosis and periodic evaluation by MRI and CT are often associated with technical difficulties related to the weight and dimensions of the patients, the cost of investigation, restricted accesibility for patients and adverse effects (irradiation). The liver biopsy is an invasive method and usually the patients are reluctant to it. Therefore another evaluation method is necessary – noninvasive, easy to perform, fast, with low cost and high accesibility – ultrasound evaluation.

Our study is trying to establish the role of ultrasound in the diagnosis and staging of the fatty liver, comparing the ultrasound evaluation with liver biopsy and another noinvasive method - statotest.

## Material and method

The study was effectuated in the Department of Radiology and Medical Imaging of the National Institute for Infectious Diseases Prof. Dr. Matei Balş, in the time frame 2008-2011 and includes a number of 390 patients, aged between 18 and 70 years, divided in two groups: group A (223 patients evaluated by ultrasound and liver biopsy) and group B (167 patients evaluated by ultrasound and steatotest).

The inclusion criteria in the study were: age over 18 years, ALT and/or AST>normal, tryglicerides > 150 mg/dl and total cholesterol > 200 mg/dl).

The serological markers evaluated included also

**Mihai Lazar**
1 Dr. Calistrat Grozovici Str., Bucharest, Romania
e-mail: mihai.i.lazar@gmail.com

platelet count, prothrombin index, ferrum and serum feritine. The steatotest combines alpha2-macroglobulin, haptoglobin, apolipoprotein A1, total bilirubin, GGT, fasting glucose, triglycerides, cholesterol and ALT, parameters adjusted for patient's age, gender, weight and height.

The equipment used was an Aloka Prosound 4000 with multi-frequency transducer (2,5/3,8/5/6 MHz). The patients were scanned in both supine and left lateral decubitus position, with subcostal and intercostal approach. All exams were performed under fasting conditions, and time - gain compensation was set to adjust the tissue echogenity as constant as possible.

The criteria used for image interpretation were: a) echogenity of portal walls, b) the degree of reflectivity from the diaphragm and c) liver echo-structure in correlation with renal cortical echogenity

The liver was staged by the most affected area in case of "geographic map" steatosis.

We awarded staging points from 1 to 4 for the first criterium and from 1 to 3 for the second and third criteria:

- **echogenity of portal walls**

1 point - incomplete contour of the 3rd degree branches of portal vein

2 points - incomplete contour of the 2nd degree branches of portal vein

3 points - incomplete contour of the 1st degree branches of portal vein

4 points - incomplete contour of main portal vein

- **the degree of reflectivity from the diaphragm**

1 point - slightly decreased reflectivity of the diaphragm

2 points - incomplete visualisation of the diaphragm

3 points - no visualisation of the diaphragm

- **liver echo-structure in correlation with renal cortical echogenity**

1 point - mild increased echogenity in comparison with the right kidney (liver echogenity ≤ kidney echogenity)

2 points - moderate increased echogenity in comparison with the right kidney (liver echogenity > kidney echogenity)

3 points - important increase of echogenity in comparison with the right kidney (liver echogenity > kidney echogenity; right kidney difficult to explore in anterior or lateral incidence)

Based on the staging points, we obtained a score and graded the liver steatosis accordingly:

$S_0$ < 3 points, $S_1$ = 3-4 points, $S_2$ = 5-7 points, $S_3$ ≥ 8 points

We compared the ultrasound staging with the staging resulted from liver biopsy (for group A) and from steatotest (for group B) in order to establish the accuracy of the ultrasound staging.

Brunt classification was used for hepatic steatosis staging:

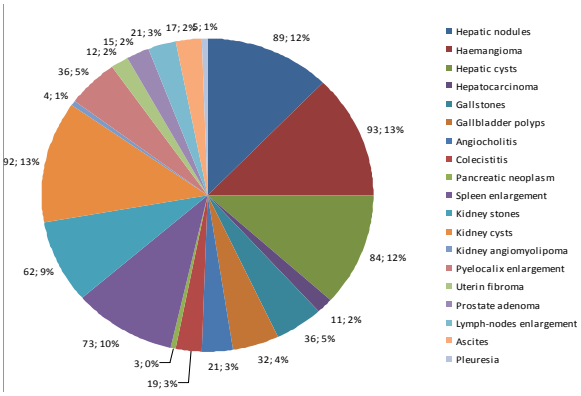
Pathological classification of hepatic steatosis (Brunt classification) [11]:

- $S_0$: Minimal steatosis, less than 5 % of hepatocytes with steatosis (felt to be non-progressive).
- $S_1$: Moderate steatosis, 6 to 32 % of hepatocytes with steatosis and lobular inflammation
- $S_2$: Important steatosis, 33 to 66 % of hepatocytes with steatosis, lobular inflammation, and ballooning degeneration
- $S_3$: Severe steatosis, 67 to 100 % of hepatocytes with steatosis, ballooning degeneration and fibrosis or Mallory bodies.

## Results

The sex ratio was aproximativ equal in both study groups with a slightly higher percent of males (53 vs 47% in group A and 56% vs 44% in group B).

The admission diagnosis in the 389 patients included in group A and group B were: chronic viral hepatitis (64%), hepatocytolic syndrome (27%) and chronic toxic-nutritional hepatitis (9%). Most frequent comorbidities of the patients, at the time of admission, included diabetes mellitus, dyslipidemia, gallstones, dyspeptic syndrome, kidney stones and hypertension.




**Graphic 1**. Ultrasound findings in groups A and B

During the ultrasound evaluation, new findings were described in 273 patients, ilustrated in Graphic 1 – which included not only hepatic disorders (nodules in 89 patients, haemangiomas in 93 patients, essential cysts in 84 patients, hepatocarcinoma in 11 cases) but also gallbladder, kidney, prostate and pancreatic affections.

For the patients in group A (Table I), we obtained similar results regarding the sensitivity and accuracy of ultrasound compared with the liver biopsy in both stages 0 and 3 (severe steatosis), having better results for stage 0. In stages 1 and 2 the sensitivity is increasing with steatosis degree.

In order to evaluate the concordance between

the two methods *Cohen's kappa* coefficient and Scott's π coefficient were also calculated, with values of 0,8876 for k and 0,8874 for π (value range from 0 to 1), suggesting a good method agreement.

The obtained specificity for ultrasound compared with the liver biopsy was over 0,90 in all stages with lower values for stage 0 and stage 2.

The PPV correlated with the prevalence for the patients in group A (Graphic 2) registers high values in stages 1 and 3, stage 2 having the lowest PPV. The NPV correlated with the prevalence for patients in group A (Graphic 3) registers high values in stages 0 and 3 (close to 1 due to the high sensitivity), followed by stage 2 and than stage 1.

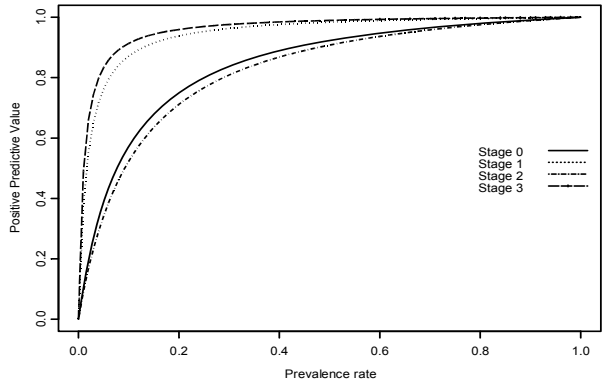
For the patients in group B (Table II), the sensitivity of ultrasound compared with steatotest was higher in stage 0 and lower for the other 3 stages, observing the same increasing tendency with the steatosis degree, as in group A. The obtained specificity for ultrasound compared with steatotest was correlated with the sensitivity value – higher in stages 0 and 3 (registering better results for stage 3) and lower in stages 1 and 2, with an increasing trend toward stage 3. The accuracy of ultrasound compared with steatotest was over 0,90 in all stages (lower than in group A), with high concordance for the patients in stages 0 and 3 (over 0,96) and an increasing accuracy with the degree of steatosis for stages 1 to 3. *Cohen's kappa* coefficient of 0,848 and Scott's π coefficient of 0,834 slightly lower than in group A, reveal also a good agreement between ultrasound and steatotest.

The PPV correlated with the prevalence for patients in group B (Graphic 4) registers high values in stages 0 and 3 (related to the high specificity), followed by stage 2 and stage 1.

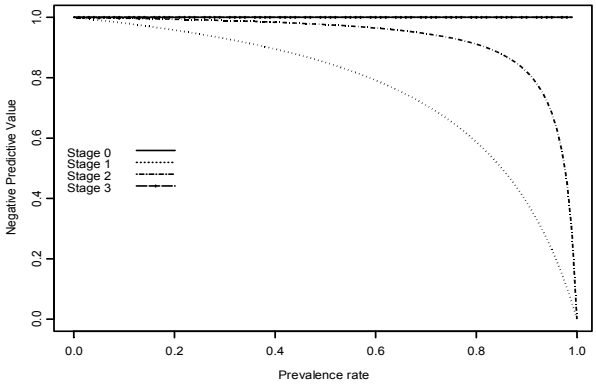
The NPV correlated with the prevalence for patients in group A (Graphic 5) shows a higher value for stage 0, followed by stage 3, stage 2 and 1 having close values with a slight lower value in stage 1.

| Parameter | Stage 0 | Stage 1 | Stage 2 | Stage 3 |
|---|---|---|---|---|
| **Sensitivity** | 1, [0.980,1] | 0.826,[0.725,0.895] | 0.978,[0.923,0.993] | 1,[0.892,1] |
| **Specificity** | 0.916,[0.741,0.976] | 0.986,[0.951,0.996] | 0.900,[0.837,0.941] | 0.989,[0.962,0.997] |
| **Accuracy** | 0.990 | 0.926 | 0.932 | 0.990 |

**Table I.** Group A - ultrasound vs. liver biopsy



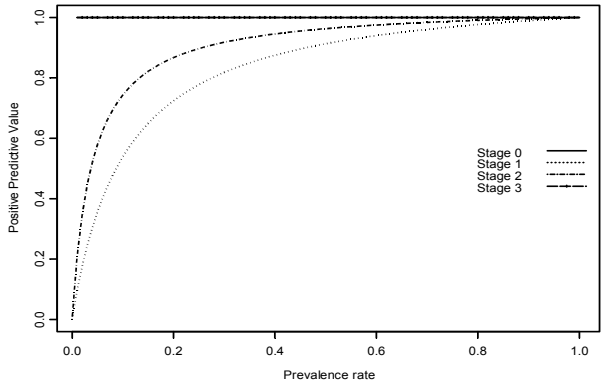

**Graphic 2**. PPV correlated with the prevalence rate in group A



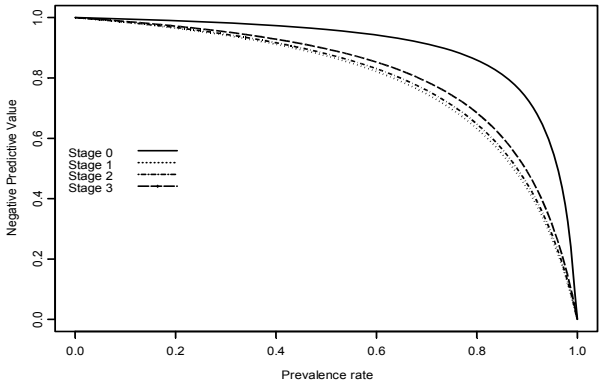

**Graphic 3**. NPV correlated with the prevalence rate in group A

| Parameter | Stage 0 | Stage 1 | Stage 2 | Stage 3 |
|---|---|---|---|---|
| **Sensitivity** | 0.959,[0.913,0.981] | 0.866,[0.738,0.937] | 0.868,[0.774,0.926] | 0.88,[0.710,0.959] |
| **Specificity** | 1,[0.831,1] | 0.917,[0.854,0.954] | 0.966,[0.906,0.988] | 1,[0.973,1] |
| **Accuracy** | 0.96 | 0.90 | 0.921 | 0.981 |

**Table II.** Group B - ultrasound vs. steatotest




**Graphic 4.** PPV correlated with the prevalence rate in group B




**Graphic 5.** NPV correlated with the prevalence rate in group B

## Discussion

Prior to every liver biopsy an ultrasound exam must be performed not only to exclude other existent pathologies such as hepatic cysts (to be further evaluated in order to exclude a hydatic cyst), haemangioma, cholangitis, but also in order to establish the liver structure - liver biopsy can provide inaccurate information if inhomogeneous steatosis is detected, due to focal fatty sparing areas.

We observed 2 patterns of "geographic map" steatosis: focal fatty infiltration - in the IV$^{th}$ segment, especially in the earlier stages of steatosis (stage 1) and patchy steatosis – in the central area of the hepatic segments while the peripheral area of the same segments was spared. The liver biopsy is usually effectuated in the lower segments of the right lobe (segment V and/or VI) in order to avoid the interception of a portal branch, hepatic vein, hepatic artery or gallbladder, therefore when focal fatty infiltration is present there is a risk for the biopsy to underevaluate the liver steatosis. In these cases we can obtain different staging by biopsy and by ultrasound because the ultrasound evaluation stages the steatosis by the most affected area and the biopsy can be effectuated in a low-fat area or in a fat-spared area. These facts can lead to an understaging tendency for liver biopsy in case of "geographic map" steatosis and to a disagreement between the ultrasound and biopsy staging. Therefore in order to improve the biopsy results a seriate biopsy or an ultrasound guided biopsy should be performed.

"The geographic map" steatosis represents not only a staging problem, it can also raise multiple differential diagnosis difficulties. Focal fatty infiltration areas or fat-spared areas may be considered dysplastic or regeneration nodules and additional CT or MRI scans are required in order to obtain additional information. In case of patchy steatosis, the ill defined hyperechoic areas which alternate with isoechoic areas can be confounded with neoplastic lesions – the hepatic vessels represent in this case a useful element, because in case of patchy steatosis there is no distortion of the hepatic vessels.

Other problems in case of grade 3 steatosis are represented by the dual mask effect of the fatty infiltration – [a)] hyperechoic lesions are very difficult to be found due to similar acoustic impedance with the surrounding fatty liver and [b)] lesions located in the posterior segments of the liver are often not detected due to the hyperattenuation of the beam. In these cases we can lower the frequency of the transducer (from 5 to 3,8 or 1,5 MHz) or consider a CT and/or MRI scan.

After the patient is diagnosed with hepatic steatosis, how soon should the ultrasound evaluation be performed again? The answer depends on the other associated pathologies of the patient. If there is no comorbidity, the patients respect the rule of 3 - long-term studies of patients with NAFLD have shown that 30% progress, 30% remain stable, and 30% improve over a 3-year period without pharmacologic intervention [12, 13], in this case we consider that an yearly evaluation is sufficient. The fatty infiltration of the liver is influenced by many factors: obesity, alcohol abuse, viral hepatitis, steroids, drugs and it's progression rate is increasing if more than one liver disease is present; also if there are associated metabolic disorders such as diabetes mellitus and hypertriglyceridemia, the fibrotic changes could be accentuated [14] and progress toward cirrhosis – in this case we recommend a 6 month evaluation.

The high sensitivity (close to 1) and high specificity (over 0,9) obtained in stage 0 are very important in order to exclude the disease. The early stages of disease – 0 and 1 usually are the most difficult to diagnose and differentiate. When examining the portal branches difficulties may appear in grading, related to the topography of the branches – while 3$^{rd}$ degree branches can be seen without problems in the anterior segments of the liver in some patients

the 3rd degree branches may have an incomplete contour in the posterior segments of the liver – in this case the patient can receive 1 steatosis point.

The results obtained for the patients in groups A and B show a good method agreement (over 0,88) between ultrasound and liver biopsy and over 0,83 between ultrasound and steatotest by both - *Cohen's kappa* coefficient and Scott's π coefficient, indicating that ultrasound can be used in the evaluation of liver steatosis and can replace successfully liver biopsy or steatotest, with similar performance.

## Conclusion

High accessibility, low cost, absence of contraindication and complication, possibility of complete liver evaluation, over 0,82 sensitivity and over 0,92 specificity compared with the liver biopsy make ultrasound a good and accurate method for staging and evaluating the liver steatosis.

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