

Classification of Early Stages of NAFLD Based on Dual Diagnostic Methods*

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Abstract

High prevalence of non-alcoholic fatty liver disease (NAFLD) has made this domain of medical diagnostics one of high professional and public interest. The major problem of NAFLD diagnostics is that in its initial phase non-alcoholic fatty liver tends to be benign without tendency to progress, while in its second phase – non-alcoholic steatohepatitis (NASH) can progress to cirrhosis, which subsequently may cause hepatocellular carcinoma. This fact explains the need for more sensitive classifications that would allow early diagnostics of NAFLD. NAFLD diagnostics in most cases is based on clinicopathological criteria – decision rules expressed through ultrasound signs and laboratory data, annotated by hepatologist/gastroenterologist. In this article we describe the process of creation of a classification of NAFLD early stages based on a decisional reasoning, which combines two methods of medical diagnostics.

Keywords: Non-alcoholic fatty liver, NAFLD diagnostics, medical ultrasound, hepatologist/gastroenterologist, pathological liver states classification.

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1 Introduction

NAFLD in its initial stage is asymptomatic, often with normal hepatic functional tests, and is difficult to diagnose [1]. It is estimated that NAFLD is the most common liver disease both in countries of Western Europe and United States with high income per capita and in poor countries [2].

NAFLD encompasses a broad spectrum of liver diseases. NAFLD is a disease that can progress, and in its natural evolution passes through several stages. It begins with free fatty acids synthesis in the liver, resulted in steatosis. Simple steatosis refers to diseases with a favorable course and possibility of a complete regression. However, in 10-20% of cases steatosis is associated with inflammation, which leads to non-alcoholic steatohepatitis [1]. In present, hepatic steatosis and steatohepatitis are considered early stages of NAFLD. The evolution of fibrosis, in turn, causes transformation into cirrhosis and cancer – advanced stages of NAFLD [2].

The degree of filling of the liver with fat can be determined using sonography technique and/or laboratory tests.

Both sonographers and hepatologists/gastroenterologists examine separately at best only functionality of the liver (most often the whole hepato-pancreato-biliary region), rather than the degree of steatosis. The degree of steatosis appears in the patients' diagnosis only if the physician finds NASH fibrosis (at best of degree 1). This is also explained by the fact that generally a hepatologist examines patients with suspected NAFLD only if they are referred by a family doctor or sonographer.

Therefore, it is impossible to determine exactly interconnection between the steatosis degree and fibrosis appearance, and the role of steatosis as a trigger.

Additionally, at the moment, there is no specialized examination algorithm and protocol (within the meaning of physicians) for patients with suspected NAFLD or patients with early stages of NAFLD.

In this paper we propose a classification using two types of findings (sonographic and hepatologic) to estimate the steatosis degree at early stages.

2 Related work

In a general way NAFLD diagnostics can be reduced to: (i) excluding the fact of alcohol consumption or its daily limitation by less than 20 g for women and less than 30 g for men; (ii) determining the presence of hepatic steatosis by imaging techniques or laboratory tests; and (iii) excluding of other liver diseases.

There are several methods of medical imagistics that can identify the degree of infiltration of the liver with fat. Ultrasound is reliable and accurate method for diagnostics of the diseases of hepato-pancreato-biliary region with sensitivity more than 70-80%. Another important advantage is that ultrasound diagnostics is by far inexpensive compared to many other imaging methods of diagnostics like MRI, CT, etc.

However, this diagnostics technique has its own drawbacks. The accuracy of ultrasound in detecting pathologies is a good one, but has some limitations, because of both false-positive and false-negative results. In addition, ultrasound images are noisy, blurred in shape, and suffer from echoes.

So, the first problem is to obtain a good image, the most relevant and useful for physician's decision-making. This is the main task of an operator, and the reason for which ultrasound investigation is considered highly operator dependent.

Ultrasound diagnostics of pathological modifications is based on the analysis of characteristic signs from images, obtained for the investigated organ. The resulting conclusion is quite subjective, and widely depends on a physician's experience. So, the second, and probably more important problem, is the interpretation of the obtained ultrasound images.

In order to solve two major problems described above, SonaRes methodology and technology for formalization of professional expert knowledge in the domain of medical ultrasound disgnotics of hepato-pancreatic-biliary region were proposed in [3].

The SonaRes knowledge base includes the following data and expert knowledge:

- the knowledge base for gallbladder contains 335 facts and 54 de-

cision rules, 166 model images annotated by the expert group, 226 images with regions of interest (ROIs) marked;

- for pancreas – 231 facts, 52 decision rules, 106 model images, 137 images with ROIs marked;
- for liver – 167 facts, 31 decision rules, 87 model images, 111 images with ROIs marked;
- for bile ducts – 257 facts, 15 decision rules, 30 model images, 37 images with ROIs marked.

On the other hand, hematologists/gastroenterologists in their professional practice use various scoring systems, which describe the hepatic functionality.

The authors of the NAFLD activity score (NAS) – Matteoni, Brunt, and the NASH Clinical Research Network Pathology Committee – proposed the best-known pathological classification of NAFLD/NASH [4-5].

The NAS represents an unweighted sum of the scores for steatosis (0-3), lobular inflammation (0-3) and ballooning degeneration (0-2). Scores of 5 or more are correlated well with the diagnosis of NASH, as confirmed by an experienced pathologist who studied the specimens independently. Scores of less than 3 are correlated equally well with "not NASH", while scores of 3 or 4 did not allow clear assignments to one or the other category.

NAS differentiates fibrosis in four stages: stage 1 means perisinusoidal fibrosis in zone 3; stage 2 is characterized by perisinusoidal and portal/periportal fibrosis; stage 3 is defined as bridging fibrosis; stage 4 reflects cirrhosis.

3 Classification of early stages of NAFLD in CATDC-NAFLD

Scenarios, describing NAFLD progress from hepatic steatosis (grade 1, grade 2, grade 3), to non-alcoholic steatohepatitis (fibrosis 0-1, fibrosis

2-3) and cirrhosis are known, and are presented in Fig. 1. Fibrosis progression in stages 0-1-2-3 is reversible, while there is no reversibility of fibrosis stage 4 (cirrhosis).

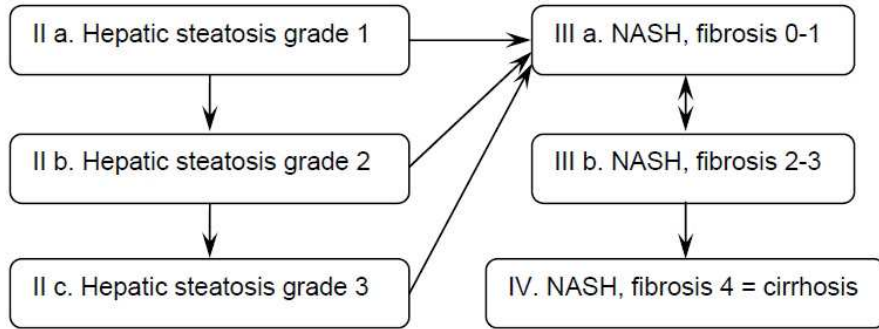


Figure 1. Scenarios, describing NAFLD progress

But, at present there is neither generally accepted theory on NAFLD pathogenesis, nor complete understanding of mechanisms of NAFLD onset and progress (its transition from steatosis to steatohepatitis). Therefore, the knowledge describing NAFLD diagnostics domain is needed to be formalized.

Discovering and formalization of knowledge diagnostics process, onset and progress of early stages of NAFLD is one of goals of CATDC-NAFLD project [6] – development of computer-aided tools for diagnostics and classification of early stages of NAFLD.

To create the knowledge base of CATDC-NAFLD we have used SonaRes technology [3], which allows to incorporate the kernel of the SonaRes knowledge base about liver pathologies into CATDC-NAFLD. This kernel includes the following data and expert knowledge: 207 facts, 38 decision rules, 81 model images, 111 images with ROIs marked.

After that, sonographic and hepatologic experts extended the number of liver rules from 38 into 44, taking into account NAFLD specifics. For diffuse hepatic steatosis 3 rules were created, identifying mild, moderate and severe forms. Also 3 rules were created for steatohepatitis, separating liver fibrosis into stages F0-F1, F2-F3 and F4. As the result

11 rules (including liver normal state) and 120 facts, corresponding to NAFLD pathologies, were selected from 44 rules and 207 facts (see Table 1).

Table 1. CATDC-NAFLD knowledge base evolution (sonographic findings)

	SonaRes liver KB	CATDC-NAFLD KB adjusted to NAFLD diagnostics
Total facts	207	120
Total rules	38	11
Total model US im- ages	81	24
Total US images with ROIs marked	111	31

The obtained 11 rules are based on sonographic findings and formulated using sonographic terminology. It can lead to misunderstanding and wrong interpretation by hepatologist.

In order to solve this problem we, together with the experts-physicians, established a correspondence between liver sonographic conclusions (rules) and NAFLD pathological states (IIa-IIc, IIIa-IIIb, IV) (see Table 2).

Validation of the obtained correspondence between liver sonographic conclusions and NAFLD pathological states was done on 10 patients.

As a result of the validation process the need for the addition of hepatologic findings based on laboratory tests was identified. It will help to make the desired classification more accurate.

An analysis of 53 liver protocols was done in order to determine characteristics, which are specific to NAFLD. The following four groups of hepatologic characteristics were identified: general data, risk factors, clinical data, and laboratory tests. The total number of hepatologic findings was essentially reduced for the case of NAFLD (see Table 3).

Thus, the base of professional knowledge, used in the diagnostics

Table 2. Classification of NAFLD pathological states

	Liver sonographic conclusion		NAFLD pathological state
1	R00. Normal liver	I	Predisposition to NAFLD
2	R20.1. Metabolic diseases. Diffuse hepatic steatosis, mild form	II a	Hepatic steatosis grade 1
3	R20.2. Metabolic diseases. Diffuse hepatic steatosis, moderate form	II b	Hepatic steatosis grade 2
4	R20.3. Metabolic diseases. Diffuse hepatic steatosis, severe form	II c	Hepatic steatosis grade 3
5	R20a. Metabolic diseases. Parcelar hepatic steatosis	II	Hepatic steatosis
6	R20b. Metabolic diseases. Diffuse hepatic steatosis with sparing areas. Focal fatty sparing	II	Hepatic steatosis
7	R20c. Metabolic diseases. Focal hepatic steatosis (pseudotumoral)	II	Hepatic steatosis
8	R24a. Steatohepatitis. Liver fibrosis F0-F1	III a	NASH, fibrosis 0-1
9	R24b. Steatohepatitis. Liver fibrosis F2-F3	III b	NASH, fibrosis 2-3
10	R24c. Steatohepatitis. Liver fibrosis F4. Liver cirrhosis	IV	NASH, fibrosis 4 = cirrhosis
11	R35. Portal hypertension	III b IV	NASH, fibrosis 2-3, NASH, fibrosis 4

of early stages of NAFLD by both sonographers and hepatologists, was obtained. This knowledge base consists of 120 facts describing NAFLD, 18 facts describing NAFLD onset risk factors and 11 decision rules. Using this knowledge base and inference engine of the SonaRes technology, early stages of NAFLD can be classified.

Table 3. CATDC-NAFLD knowledge base evolution (hepatologic findings)

	Total hepato- logic findings	NAFLD- related findings
General data	6	4
Risk factors (no alcohol-related, used only for NAFLD progression scenarios)	29	18
Clinical data	36	2
Laboratory tests	55	14
Total	126	20 (+18)

4 Conclusions and future work

The current practice is the following: a hepatologist generally only assesses patients after they are referred by the ultrasound physician. But not always ultrasound images can show the liver pathological changes in the early stages of NAFLD, or ultrasound physician pays attention to more serious pathology in gallbladder, pancreas and biliary system. It is a major cause of delayed access to the hepatologist and late NAFLD diagnostics. The proposed classification allows to focus attention on the early liver pathological changes, revealed not by one, but by two main diagnostics methods, that improves the accuracy of diagnosis and allows to diagnose early stages of NAFLD. In addition, this classification forces ultrasound physician and hepatologist to cooperate at NAFLD early stages manifestation.

As in the inference mechanism we use decision rules that involve sonographic findings, obtained from physicians-experts, and case-based hepatologic findings, it is necessary to validate the obtained inference on the same cohort. Another task for the future work is to create a score, taking into account both sonographic and hepatologic findings.

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