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***Clinical significance of ultrasonography in evaluation***

***of morphofunctional state of liver and portohepatolienal***

***bloodstream in chronic diffuse liver diseases***

**Abstract:** In randomized three-phase prospective cohort controlled research

which included 2564 persons with chronic diffuse liver diseases (1865 cases of fatty

liver disease, 462 cases of chronic hepatitis, 100 cases of liver cirrhosis) and 137

healthy controls, the clinical significance of ultrasonography in quantitative evaluation

of liver parenchyma morphofunctional state and portohepatolienal bloodstream in

patients with chronic diffuse liver diseases was estimated. Twenty-seven ultrasound

and two additional, derived from laboratory tests index parameters were testified for

the grounding to be included into diagnosis-prognostic algorithm for patients with this

pathology, which has been developed, validated and recommended for practical

application. Further perspectives are related to fundamental logico-statistical analysis

of the data for development of mathematic model of pathologic process and its

application to practical health care service.

***Keywords:*** Fatty liver disease, chronic hepatitis, liver cirrhosis, ultrasound

diagnosis, prognosis.

Chronic diffuse liver diseases cause not only significant medical problem,

promoting portal hypertension, hepatocellular failure, oncological diseases etc. [1],

but also social and economical, associated with loss of ability to work in active

population; particularly, mortality due to liver cirrhosis in European countries vary

from 100 to 400 per 1 million of male population and from 40 to 150 per 1 million

among females [2, 3, 4, 5].

In last decade is an impetuous development of chronic diffuse liver disease

takes place. Technical progress, improvement of hardware and software have made

it possible to significantly go forward in understanding of etiology and pathogenesis

of hepatobiliary pathology, noticeably improve treatment results. In many respects

these changes became possible only due to introduction and development of new

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highly-technological methods of radiation (visual) diagnosis in general and

ultrasonography – as well [6, 7].

Results of radiological diagnostic methods are widely used in order to build

prognostic models and calculate a prognosis in each certain clinical case about

functional compensation of liver, presence of indications for radical intervention etc.

[8]. Both mathematical [9, 10, 11, 12] and virtual [13], dimentional models based on

morphological investigation of liver come in handy and give an opportunity to more

exactly and objectively evaluate changes which develop in vivo, formulate an

individual prognosis for a patient.

Despite the availability of wide spectrum of other modern non-invasive and

low-invasive radiation methods of diagnosis for chronic diffuse liver diseases,

ultrasonography does not lose its topicality and is the leader of practical application in

public health service. Undoubted perspective is characteristic for methods which

base not only on immediate primary results of investigation, but on results of their

further objectivization using mathematical modeling and building of prognostic model

of the pathological process. Reasonability of ultrasonography application for

diagnosis of chronic diffuse liver diseases is related to its following characteristics:

non-invasive [14], safe [15], easily done [16], relatively cheap and capable to

simultaneous evaluation of comorbid pathology [17], also in dynamics, reproductible

and precise, standardized [18], easily combined with other methods [19, 20], capable

for further improvement, including contrast-enhance.

While, some limitation of ultrasonography in diagnosis of chronic diffuse liver

diseases takes place in medical practice [21, 22]. This problem may be solved by

improvement of ultrasonography diagnosis approach with automation of image

analysis [23], introduction of index parameters etc.

Thus, despite general success of ultrasonography in diagnosis of chronic

diffuse liver diseases, till nowadays improving of this approach remains vital.

**Aim** of research – optimization of diagnosis of chronic diffuse liver disease by

improving of ultrasonographic approach with evaluation of diagnostic power and

information capacity of its parameters.

**Materials and methods.** On first phase an estimation of diagnostic

capabilities (values) of ultrasonography in chronic diffuse liver diseases was

performed. It included investigation of 103 cases of chronic diffuse liver disease: fatty

liver disease (n=63), chronic hepatitis (n=12), liver cirrhosis (n=28), cases with intact

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liver (control group, n=2). This phase was conducted on the base of Kharkiv Regional

Clinical Hospital – Center of Emergency Medical Care and Disaster Medicine in

2012–2013 with the aim of evaluation of accordance of ultrasonographic data with

results of liver autopsy (both n=105).

Second phase was aimed on development of a diagnosis-prognostic algorithm

of ultrasonography application and profound instrumental-laboratory tests (apart of

ultrasound – anamnestic and physical data collection, complete blood count and

biochemical blood tests) were performed. Two hundred fifty three persons, including

patients with fatty liver disease (n=142), chronic hepatitis (n=43), liver cirrhosis

(n=27), and 50 healthy people shared this phase of the research. It has been

conducted in clinical hospital of Grigoriev Institute of Medical Radiology of National

Academy of Medical Science of Ukraine in 2013–2014. All participants underwent

detailed repetitious instrumental and laboratory investigations. In this cohort male

and female age medians did not significantly differ.

Third phase was most large in the research as aimed on evaluation of

ultrasonography capabilities in prospective evaluation of chronic diffuse liver disease

course by validization of developed diagnosis-prognostic algorithm for pathologic

process severity evaluation and course prediction, and also building a mathematic

model of pathologic process. In order to reach the goal, 2206 persons were

examined, including patients with fatty liver disease (n=1660), chronic hepatitis

(n=416), liver cirrhosis (n=45), control healthy individuals (n=85). This phase of the

research was performed on the base of LTD Medical Diagnostic Center «Expert-

Kharkov» in 2013–2014. Age median was 56.1 (47.1; 64.1) years, 55.0 (44.3; 64.2)

years in men, 56.4 (47.7; 64.1) years in women (difference is reliable by р=0,053).

Ultrasound investigation was performed with Xario SSA 660A system (Toshiba

Medical Systems, Japan). Pathomorphological investigation has been conducted

according to standard protocols with evaluation, where applicable, of liver steatosis

[24] and liver fibrosis intensity degree [25], level of activity (Knodell R. G., 1981).

Nonparametric methods of statistical analysis were applied [26]. Median (Mе) and

interquartile interval with representing lower, 25 %, quartile (LQ) and upper, 75 %

quartile (UQ) were calulated, result was expressed by Me (LQ; UQ) way for

shortness. Kruskal-Wallis ANOVA & median test method, Mann-Whitney U-criterion,

Wilcoxon method, correlation by Spearman, Fisher angular transformation were used

where applicable. Comparative analysis in groups of separate diagnostic criteria

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distribution using ANOVA and Wald sequential analysis (Wald A., 1947) in its

interpretation for medical diagnosis (Genkin A. A., 1962; Gubler E. V., 1978) by

ranging of parameters by their differential-diagnostic information capacity allowed to

define diagnostic value, prognostic significance and influence power of factors on

parameters divergence in clinical groups and prognostic coefficients. Only

independent prognostic parameters were included in the algorithm. In cases when

correlation strengths between factors was more than |0,70|, one of factors was

excluded from list of parapeters. Ranking of parameters by influence strengths,

evaluation of prognostic and information capacity of parameters allowed to choose

the most reliable parameters. At the last phase, mathematic modeling using

discriminant analysis and building of artificial virtual neural networks with their further

training was performed.

**Results and discussion.** In 1st phase the age median was 62 (46; 71) years

without significant gender differences, while gender comparisons in different

nosologic groups showed the age difference (р=0.0001) – the oldest in fatty liver

disease group, 64.0 (60.0; 73.0) years; youngest in chronic hepatitis group, 41.6

(31.0; 52.5) years; intermediate in liver cirrhosis group, 52.0 (41.5; 65.5) years. Age

comparison in different nosologic groups in further phases showed above mentioned

(in 1st phase) differences in general and among women (both р<0.001).

Pathomorphological verification of ultrasonography results in evaluation of

disease character in patients with chronic diffuse liver diseases revealed 1.9 %

probability of false-positive ultrasound diagnosis of this pathology, diagnostic

capacity of 14–97 % (with central value of 56 %).

Using results of profound clinical, instrumental and laboratory investigation

including frequency of separate ultrasonography parameters and prognostic value of

each of criterion the screening algorithm was elaborated in order to predicting of

complication risk. It has table form, which includes demographic-antropometric (age,

gender, body mass index), sonographic (liver size, characteristics of capsule,

parenchyma, ascites, hepatic vein circulation, caudal to right lobe transverse size,

degree of steatosis, congestion index, modified hepatic index, hepatic vascular index,

index of arterial perfusion, portolienal venous index, pulsatory index of spleen artery,

platelets to spleen diameter ratio, right lobe width to albumins ratio) parameters,

appropriate prognostic coefficients and prognostic result evaluation scale. By each

parameter its presence or absence has to be evaluated, corresponding prognostic

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coefficients are to be summarized. By achievement of threshold sum of coefficients a

risk group was stated by using the scale: if equal or less than -19.8, risk is minimal; if

more than -19,8 and less than 19.8, risk is uncertain; if equal or more than 19.8, risk

is high.

For each of three diseases canonic discriminant functions were built. Predicted

appliance to groups of low, uncertain, high progression risk in fatty liver disease was

78.9 %, 69.3 %, 99.7 % accordingly; in chronic hepatitis – 63.7 %, 61.1 %, 93.2 %

accordingly; in liver cirrhosis – 93.1 %, 64.8 %, 99.7 %.

Neural networks (three-level perceptron with descending number of nodes)

were built, trained and sensitivity, specificity evaluated. After training the square

below ROC-curve to each of risk groups became increased > 80 %.

**Conclusions.** 1. Prospective randomized three-phase populational (on 3rd

phase) research has proved the clinical significance of ultrasonography in evaluation

of morphofunctional state of liver and portohepatolienal bloodstream in chronic

diffuse liver diseases (fatty liver, chronic hepatitis, liver cirrhosis).

2. Diagnosis-prognostic algorithm which includes anthropodemographic,

clinical and ultrasonographic parameters has been elaborated, intending on forecast

of risk of unfavourable course of chronic diffuse liver diseases.

3. Predicting value of ultrasonography has been boosted by discriminant

mathematic model development, artificial virtual neural networks application.

4. Longitude multicenter study of proposed approach in diagnosis of chronic

diffuse liver disease using non-invasive ultrasonography and evaluation of treatment

efficacy might be further perspectives of the research.

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