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DIAGNOSTIC POSSIBILITIES OF LIVER ELASTOGRAPHY

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Introduction: The review deals with the aspects of noninvasive instrumental diagnosis of diffuse liver diseases on the fibrosis and cirrhosis stage, which is characterized by tendency to progression and the rapid development of complications. Contemporary data of the studies results on the most popular methods of elastography are presented.

Aim of our review was to analyze the published data of the modern methods of diagnosis of liver fibrosis and cirrhosis.

Materials and Methods: Selection of publications using the key words was performed in PubMed Medline database and scientific search system Google Scholar.

Results: There are different opinions of the authors about the pros and cons of Transient elastography (TE) and Acoustic Radiation Force Impulse (ARFI). However, the scope of studies and clinical diagnostic aspects in TE greatly exceeds the number of those for ARFI.

Conclusions: Issues of determining of effective non-invasive instrumental methods in patients with chronic liver diseases remain to be actual.

Keywords: liver fibrosis, liver cirrhosis, transient elastography, acoustic radiation force impulse

ДИАГНОСТИЧЕСКИЕ ВОЗМОЖНОСТИ ЭЛАСТОГРАФИИ ПЕЧЕНИ

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Введение: Обзор посвящен аспектам неинвазивной инструментальной диагностики диффузной патологии печени на стадии фиброза и цирроза, которые характеризуются склонностью к прогрессированию и быстрым развитием осложнений. Приведены современные данные результатов исследований, посвященных изучению наиболее популярных методов эластографии.

Цель: Анализ литературных данных о современных способах диагностики фиброза и цирроза печени.

Материалы и методы: проведен поиск публикаций с применением ключевых слов в базе данных PubMed Medline и в научной поисковой системе Google Scholar.

Результаты: Существуют различные мнения авторов о преимуществах и недостатках транзиентной эластографии (ТЕ) и акустической импульсно-волновой эластографии (ARFI) в диагностике фиброза и цирроза печени. Однако объем исследований и клинико-диагностических аспектов в области ТЕ в значительной мере превышает число таковых для ARFI.

Выводы: Вопросы определения эффективных неинвазивных инструментальных методов обследования пациентов с хронической патологией печени остаются актуальными.

Ключевые слова: фиброз печени, цирроз печени, транзиентная эластография, акустическая импульсно-волновая эластография

БАУЫР ЭЛАСТОГРАФИЯСЫНЫҢ ДИАГНОСТИКАЛЫҚ МҮМКІНДІКТЕРІ

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Кіріспе: Шолу жедел прогрессияға және асқынуға бейімді фиброз және цирроз сатасындағы бауырдың диффузды ауруларын инвазивті емес инструментальді диагностикасының өзекті мәселелеріне арналған. Эластографияның ең көп тараған әдістеріне арналған зерттеулердің нәтижелері көрсетілген.

Берілген әдебиеттік шолудың **мақсаты** - бауыр фиброзы мен циррозы туралы заманауи диагностикалық әдістері жайлы әдебиеттерді тауып, соған талдау жасау.

Материалдар мен әдістер: негізгі сөздерді қолдана отырып PubMed Medline мақалалық базасында және Google Scholar ғылыми іздеу жүйесі көмегімен жүргізілді.

Нәтижелері: Транзиентті эластография (ТЕ) мен акустикалық импульс толқынды эластография (ARFI) артықшылықтары мен жетімсіздіктері жайында авторлардың пікірі біркелкі емес. Сонымен бірге ТЕ саласындағы зерттеулердің көлемі мен клиника-диагностикалық аспектілері ARFI-ге қарағанда неғұрлым жоғары.

Қорытынды: Бауырдың диффузды ауруларынының тиімді инвазивті емес инструментальді диагностикасына байланысты сұрақтар өзекті болып табылады.

Негізгі сөздер: бауыр фиброзы, бауыр циррозы, транзиентті эластография, акустикалық импульс толқынды эластография.

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Chronic liver diseases may develop as a result of various injurious agents like Hepatitis viruses B & C, alcohol consumption, autoimmune disorders, certain medicines, metabolic disorders including iron, cupper and fat injury, obesity and others. Chronic liver disease with or without fibrosis comprise a wide spectrum of clinical conditions ranging from the asymptomatic state, that is usually accidentally discovered to the emergence of cirrhotic or end stage liver disease manifestations. Portal hypertension is almost an inescapable outcome of liver cirrhosis which is present clinically with ascites, and esophageal or gastric varices, that frequently lead to disastrous bleeding [9]. Spontaneous bacterial peritonitis, encephalopathy, hepato-renal syndrome are other serious manifestations of the disease.

Liver biopsy remains to be considered as the “gold standard” of diagnosis of chronic hepatopathies. The most popular fibrosis staging system is METAVIR, which is represented by five stages: F0 (no fibrosis), F1 (portal fibrosis without septa: minimal fibrosis), F2 (portal fibrosis with few septa: moderate fibrosis or clinically significant fibrosis), F3 (septal fibrosis with many septa but no cirrhosis: severe fibrosis) and F4 (cirrhosis). Most of non-invasive tests adapted their scoring scales in according to this classification.

Liver biopsy has several drawbacks including the significant morbidity (3%) and mortality (0.03%) that it carries [10]. Liver biopsy is also known for its sampling errors, with inter-observer and intra-observer diagnostic discrepancies,

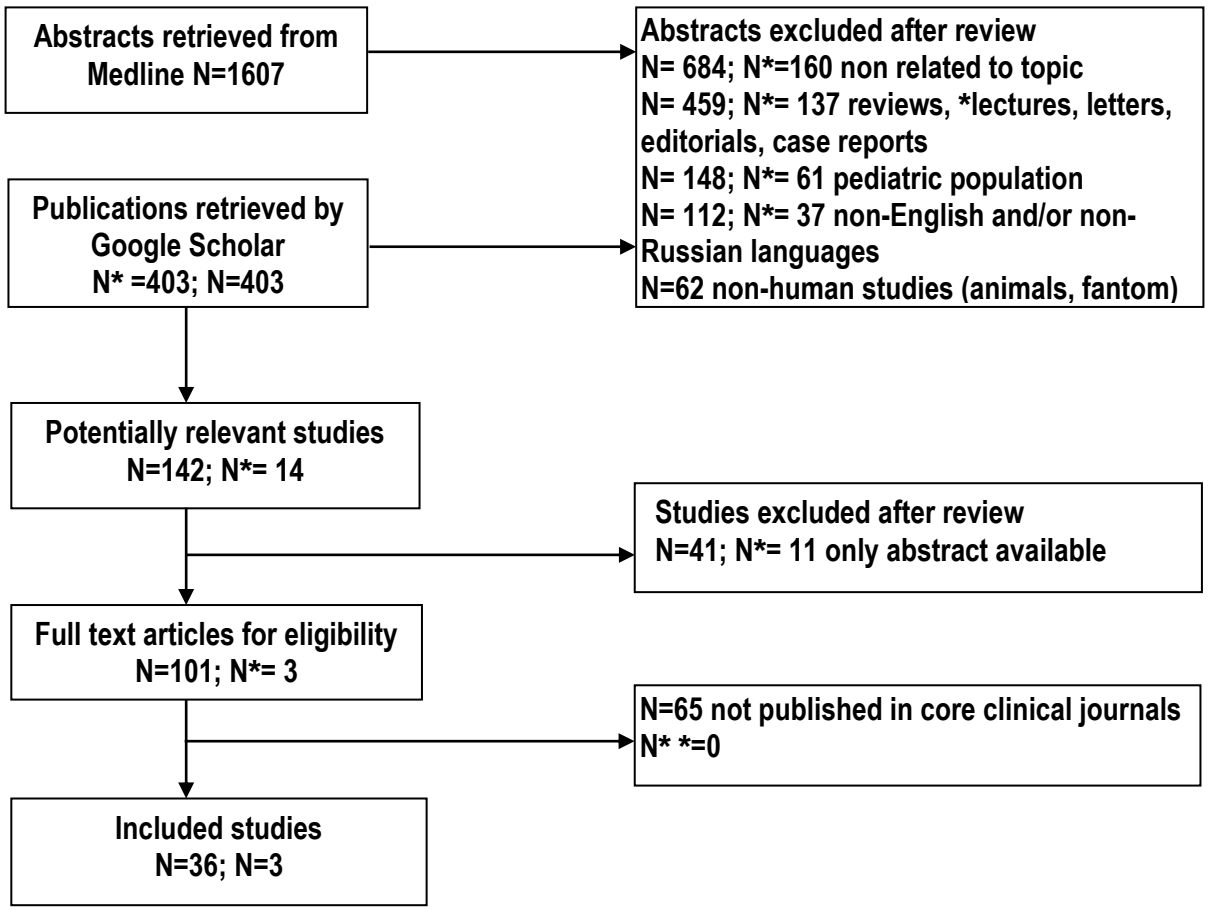
which makes it of limited benefit both in clinical practice and medical research [6, 32]. Evaluation of portal hypertension and esophageal varices by HVPG and endoscopy is also limited by their invasiveness although they are known as the gold standard techniques in this respect [8].

Non-invasive imaging tests for evaluation of liver fibrosis have been developed. Some procedures were introduced as an alternative for hepatopathological evaluation these included laboratory, which use different combinations of marker indices from the serum [1]. As the imaging methods the ultrasound waves are utilized in determining virtual transient elastography of the liver as an indicator of fibrotic, steatotic and cirrhotic changes [22].

Berzigotti A. et al. divided all the ultrasound techniques of liver fibrosis evaluation to two large groups [7]. The first group comprises the well-validated methods such as grey-scale ultrasound, colour-and-power Doppler, pulse wave Doppler US, transient elastography. Another group is represented by novel techniques which need validation: high-frequency grey scale ultrasound, real-time elastography, acoustic radiation force impulse imaging, shear-wave elastography

This review collects the data on the most widely used imaging methods for the non-invasive diagnosis of liver fibrosis, with particular accent on transient elastography and acoustic radiation force impulse imaging. The process of including the articles to this review is shown on Figure 1.

Figure 1: Review flow diagram



N - Abstracts retrieved from Medline

N***** - Publications retrieved by Google Scholar on Russian

N*** *** - Publications retrieved by Google Scholar on Russian were not checked for publishing in core clinical journals due to the lack of information on this language; all of them were included to review

Transient elastography

Technique

Transient Elastography (TE) (FibroScan, Echosens, Paris, France) is a dynamic quantitative technique which uses acoustic waves with frequency 50 MHz, generated by external probe [5]. Liver stiffness (LS) measurement is performed in the right lobe, with patient in supine position, by intercostal approach, with the right arm in maximum abduction. At least 10 valid measurements must be obtained, with a success rate (SR = ratio of the number of successful acquisitions divided by the total number of acquisitions) ≥ 60% and a ratio of the interquartile range interval (IQR=the difference between the 75th and 25th percentile, essentially the range of the middle 50% of the data) <30%. Liver elasticity is expressed in kilopascals (kPa).

Clinical applications

There are several studies dedicated to liver stiffness measurements in **normal** people assessed by TE (Table 1) [15, 16, 23, 25, 34, 35]. The vast majority of study participants are represented by Europeans.

Table 1.

Normal values of LSM by TE.

	Roulot D.	Colombo S.	Sirli R.	Corpechot C.	Fung J.	Kim S.
Number of study participants	429	327	152	71	28	69
Population	Medical check-up	Blood donors	Healthy volunteers	Healthy volunteers	Healthy living-related liver donors	Living kidney and liver donors
LS value (KPa)	5.4 ±1.5 *	4.9 ±1.7 *	4.8 ±1.3 *	4.8 (2.5-6.9)**	4.6 (2.0-7.1) **	3.9-5.3 ***

* mean±SD

** median (range)

*** fifth and 95th percentiles

Initially, TE was applied in patients with **chronic hepatitis C**. Some studies shown that the AUROC of TE ranged from 0.77 to 0.90, with a cutoff value of 6.2-8.7 kPa for assessment of significant fibrosis (F≥2), and an AUROC of 0.90-0.97 and cutoff value of 9.6-14.8 kPa for assessment of cirrhosis [4, 12, 30, 39].

In 202 **chronic hepatitis B patients** liver fibrosis was evaluated by means of liver biopsy and TE. It was shown that these two methods significantly correlated (r=0.65, *P*<0.001) with ROC curves for F≥2, F≥3 and F=4 indicating 0.81, 0.93 and 0.93 respectively[28]. Sporea et al showed that a significant direct correlation between LS measurements and fibrosis was found in HBV patients (*r* =0.408, *P* <0.0001) [37].

Chan et al. have shown that liver stiffness readings increase in patients with chronic hepatitis B and C with **elevated ALT**: for predicting severe fibrosis (F ≥ 2) – 9 kPa in patients with normal ALT and 12 kPa in patients with ALT higher than 5 times the upper limit of normal; and for predicting liver cirrhosis (F=4) – 12 kPa in patients with normal ALT and 13.4 kPa in those with high ALT [13].

Fibroscan is still being validated in patients with **NAFLD** due to the high failure rate due to invalid measurements in overweighed or obese patients. The using of standard M-probe was followed with 14-17% failure rates [11, 31]. For the more accuracy of TE measurements in obese patients the XL-probe with the frequency 50 MHz and 35-75 mm depth was suggested [19, 29]. Controlled attenuation parameter (CAP) has been offered as a noninvasive method for detection and quantified measurement of hepatic steatosis. Some studies showed that CAP was a good tool for efficient separation of steatosis grades [14, 18].

Pavlov Ch. Et al showed that transient elastography as an efficient tool of non-invasive diagnostics of liver fibrosis for the screening in the patients presenting with hepatic pathology in Moscow [2]. But another study of these research group demonstrated that performance of TE is restricted with BMI≥28 [3].

Another limitation of using the TE in patients with CLD is the impossibility to obtain in patients with ascites because the elastic waves are unable to propagate through liquids. On the other hand several studies have shown the similar performance of TE and hepatic venous pressure gradient for predicting the **portal hypertension** [33].

Acoustic Radiation Force Impulse Technique

By short-duration acoustic radiation forces (with a transmission frequency of 2.67 MHz), it generates localized displacements in a selected region of interest (ROI; a box with dimension of 1 cm × 0.5 cm chosen while performing conventional B-mode) at depth of 8 cm. Patients should be supine, with the right arm in maximum abduction. Probe is placed parallel to the intercostal space. 5-10 measurements are performed in the right lobe, with the patient holding his/her breath gently. The measurement (m/s) is displayed on the screen after a moment. The results of measurements of ARFI being expressed in m/s could be converted into kilo Pascal (kPa) using the Siemens software for being comparable with TE results in the same patient.

Clinical application

Mean **normal** values for ARFI range about 0.8-1.56 m/s [17, 27].

Similar with TE, ARFI was first used and validated in patients with **chronic hepatitis C.** According to study of Freidrich-Rust et al. the best LS cut-off values assessed by ARFI for predicting F≥2, F≥3 and F=4 were: 1.35 m/s, 1.55 m/s and 1.75 m/s respectively [21].

Sporea et al showed that the mean liver stiffness values of the same stage of fibrosis obtained by ARFI were similar between patients with **chronic hepatitis B** and those with chronic hepatitis C [36]. In another study of these authors a significant direct correlation between LS measurements and fibrosis in HCV patients (Spearman's r =0.578, P<0.0001) was detected [37].

The range of studies was dedicated to evaluate the diagnostic capability of ARFI in **NASH/NAFLD** patients. Kuroda H. et al. proposed the option of ARFI combination with the calculation of the special indicators acoustical structure quantification and focal disturbance ratio to identify NAFLD invivo [26]. Guzman-Aroca et al performed the ARFI measurements in 32 asymptomatic patients with morbid obesity for differentiating NAFLD from NASH [24]. Some studies reported that inflammation increase LS measurement in NAFLD patients [20, 38].

Conclusion

The comparative characteristics of TE and ARFI are presented on Table 2.

Table 2.

Comparative description of TE and ARFI.

Characteristics	Transient Elastography	Acoustic Radiation Force Impulse
Requirement of special device	Needs a dedicated machine	Used as implementation to conventional US systems
Possibility of ROI selection	Cannot be chosen by operator	Chosen by operator
Units	kPa	m/s (can be be converted into kilo Pascal (kPa) using the Siemens software)
Range of values	High	Narrow
Applicability for patients with obesity or ascites	Low	High
Discrimination between transitional stages of fibrosis	Unable	Unable
Performance for significant fibrosis and cirrhosis	High	High
Validation	Well-validated	Needs validation

In conclusion of our short review on liver elastography using, we can say that the elastographic methods showed good results for the assessment of liver stiffness. TE is increasingly used in daily practice while the other elastographic methods try to prove their value in clinical studies.

Nowadays the diagnostic value of liver elastography has been widely discussed in a large number of studies abroad. However, there is a shortage of researches dedicated to technical aspects and clinical appliances in Newly Independent States, especially in our country.

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