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ИСПОЛЬЗОВАНИЕ УЛЬТРАЗВУКОВОЙ ШКАЛЫ ВЫРАЖЕННОСТИ СТЕАТОЗА ПЕЧЕНИ В ДИАГНОСТИКЕ АТЕРОСКЛЕРОЗА ПЕРИФЕРИЧЕСКИХ АРТЕРИЙ У ПАЦИЕНТОВ С НЕАЛКОГОЛЬНОЙ ЖИРОВОЙ БОЛЕЗНЬЮ ПЕЧЕНИ

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Ultrasound Score of Liver Steatosis Severity in the Diagnosis of Peripheral Arterial Atherosclerosis in Patients with Nonalcoholic Fatty Liver Disease

Резюме

Неалкогольная жировая болезнь печени (НАЖБП) является широко распространенным заболеванием, тесно ассоциированным с ожирением и метаболическими нарушениями. В диагностике неалкогольной жировой болезни печени большое внимание уделяется неинвазивным инструментальным маркерам. **Целью** настоящего исследования было изучение взаимосвязи значений ультразвуковой шкалы стеатоза Hamaguchi с распространенностью атеросклероза периферических артерий, а также оценка диагностической ценности Hamaguchi score в отношении наличия стенозов сонных артерий и артерий нижних конечностей. **Материалы и методы**. Всем участникам проводили дуплексное сканирование артерий каротидного бассейна и артерий нижних конечностей, абдоминальное ультразвуковое исследование. **Результаты.** В исследовании приняло участие 175 пациентов, среди них 72 мужчины и 103 женщины. Медиана возраста пациентов составила 50 лет. Сочетанный атеросклероз сонных артерий и артерий нижних конечностей выявлен у 76 (43,4 %) пациентов. Медиана выраженности стеатоза печени по шкале Hamaguchi составила 2 балла. В группе пациентов с сочетанным атеросклерозом сонных артерий и артерий нижних конечностей были отмечены достоверно более высокие значения Hamaguchi score (p=0,026). По данным логистического регрессионного анализа увеличение балла по шкале Hamaguchi на одну единицу ассоциировалось с увеличением относительного риска выявления сочетанного атеросклероза двух бассейнов (сонные артерии и артерии нижних конечностей) в 1,192 раза (95 % ДИ 1,023-1,387). По данным ROC-анализа увеличение значений шкалы Hamaguchi более 2 баллов позволяло диагностировать сочетанные стенозы каротидных артерий и артерий нижних конечностей с чувствительностью 52,6 % и специфичностью 63,6 % (AUC=0,596; p=0,024). **Заключение.** У пациентов с неалкогольной жировой болезнью печени значения шкалы Hamaguchi более 2 баллов позволяет диагностировать сочетанные стенозы каротидных артерий и артерий нижних конечностей с чувствительностью 52,6 % и специфичностью 63,6 %.

Ключевые слова: *неалкогольная жировая болезнь печени; атеросклероз периферических артерий; шкала Hamaguchi*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract
Non-alcoholic fatty liver disease (NAFLD) is a widespread disease closely associated with obesity and metabolic disorders. Noninvasive instrumental markers are of great importance in the diagnosis of NAFLD. **The aim** of the present investigation was to study the correlation of Hamaguchi score with the prevalence of peripheral arterial atherosclerosis and to evaluate the diagnostic value of Hamaguchi score in relation to the presence of carotid and lower limb arterial stenoses. **Materials and Methods.** All the participants underwent duplex scanning of the arteries of the carotid basin and the arteries of the lower extremities, and abdominal ultrasound examination. **Results**. The study involved 175 patients, including 72 men and 103 women. Median age of the patients was 50 years. Combined atherosclerosis of carotid arteries and the arteries of the lower extremities was detected in 76 (43,4 %) patients. Median severity of hepatic steatosis according to Hamaguchi score was 2 points. Significantly higher Hamaguchi score values (p=0,026) were observed in the group of patients with combined atherosclerosis of carotid arteries and lower limb arteries. According to logistic regression analysis, a one unit increase in Hamaguchi score was associated with a 1,192-fold (95 % CI 1,023-1,387) increase in the relative risk of finding combined atherosclerosis of two basins (carotid and lower extremity arteries). According to ROC-analysis, increasing Hamaguchi score>2 points allowed to diagnose combined stenoses of carotid and lower limb arteries with sensitivity of 52,6 % and specificity of 63,6 % (AUC=0,596; p=0,024). **Conclusion**. In patients with NAFLD the Hamaguchi score>2 made it possible to diagnose combined stenoses of the carotid and lower extremity arteries with a sensitivity of 52,6 % and specificity of 63,6 %.

Key words: *nonalcoholic fatty liver disease; peripheral arterial atherosclerosis; Hamaguchi score*

Conflict of interests
The authors declare no conflict of interests

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AUC — area under the curve, FLI — fatty liver index, LFS — Liver Fat Score, ROC — receiver operating characteristic, CI — confidence interval, CHD — coronary heart disease, II — interquartile interval, Me — median, NAFLD — non-alcoholic fatty liver disease, TCS — total cholesterol, GFR — glomerular filtration rate, TGs — triglycerides, HDL cholesterol — high density lipoprotein cholesterol, LDL cholesterol — low density lipoprotein cholesterol

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a common disease which is closely associated with obesity and metabolic disorders [1-3]. However, this condition can be observed also in persons with normal body weight: in general, approximately 40 % of NAFLD patients have normal body mass index [4]. This fact is important to understand the significance of this disease. Results of recent metaanlyses show a high risk of fatal and non-fatal cardiovascular events (myocardial infarction, stroke, revascularisation) in groups of NAFLD patients, irrespective of the presence or absence of metabolic syndrome and obesity [5, 6]. It is important to note that cardiovascular diseases were the main cause of deaths in NAFLD patients (38 % of all causes) in the studies conducted in the USA, Europe and Asia [7, 8].

In NAFLD diagnosis, a greater emphasis is put on noninvasive laboratory and instrumental markers (in particular, on fatty liver index (FLI), hepatic steatosis index (HSI), Hamaguchi score). Often these parameters are used as a means to search for correlations between NAFLD and cardiovascular diseases. Biyao Zou et al. (2021) noted a higher incidence of atrial fibrillation, coronary heart disease (CHD), stroke, cardiac failure, and also statistically higher cardiovascular death rates (10.42 per 1000 person years, 95 % CI 10.15–10.70 vs. 5.18 per 1000 person years, 95 % CI 5.04–5.32) in patients with FLI > 60 vs. patients with FLI < 60 [8]. A study by Chenxi Wang et al. (2021) demonstrated that an increase in HSI by one quartile was associated with 1.16-fold increase in the odd ratio (OR) to diagnose carotid atherosclerosis (95 % CI 1.114–1.207) [9]. A number of researchers noted a close correlation between endothelial dysfunction markers, in particular vascular endothelial growth factor, and HSI values [10]. Also a correlation between impaired lipid metabolism and ultrasound steatometry indices was established: Daniele Pastori et al. (2018) found that Hamaguchi score (semi-quantitative ultrasound hepatic steatosis

scale) statistically correlated with the remnant cholesterol concentration [11].

Literature data analysis demonstrates that noninvasive steatosis markers can be an efficient tool for cardiovascular risk stratification and search for associations with cardiovascular complications. The objective of this study was to analyse the correlation between Hamaguchi ultrasound steatosis score and the incidence of peripheral arterial atherosclerosis; and to evaluate the diagnostic value of Hamaguchi score in relation to carotid steatosis and arterial steatosis of lower limbs.

Materials and methods

The study enrolled 175 patients (72 male subjects and 103 female subjects) with ultrasound verified NAFLD. Median age was 50 (44.0; 56.0) years old.

All subjects signed a voluntary informed consent form. Subjects with the following conditions were excluded from the study: acute cardiovascular event (acute coronary syndrome, acute cerebrovascular event, transient ischaemic attack), stage C4–C5 chronic kidney disease (CKD), malignancies, hepatic cirrhosis, viral hepatitis. The study protocol was approved by the Local Ethics Committee (Meeting Minutes No. 10 dated 27 October 2018).

NAFLD was diagnosed using the generally accepted criteria: excessive fatty deposits in the liver found during ultrasound examination; no history of chronic consumption of toxic doses of alcohol [12].

All subjects underwent a duplex ultrasonography screening of carotid system arteries and lower limb arteries. For a full report on peripheral artery ultrasound examination, please see our previous articles [13]. Percentage of artery stenosis was measured planimetrically in B mode using the vessel cross section diameter and haemodynamic criteria. Stenosis was measured under the ECST (The European Carotid Surgery Trial) method. ≥ 50 % carotid stenosis was diagnosed if the following criteria were met: peak systolic velocity (PSV) > 125 cm/s; the ratio of internal carotid artery (ICA) PSV and the common carotid artery PSV > 4; ICA end-diastolic velocity > 40 cm/s [14,15]. ≥ 50 % lower limb artery stenosis was diagnosed if the following criteria were met: an increase in PSV up to 200–400 cm/s; spectral dilatation in the stenotic area; biphasic blood flow [16].

Abdominal ultrasound was performed using Canon Aplio 400 (Japan); a 2.5–5 MHz curved transducer was used. The standard ultrasound signs of hepatic steatosis were evaluated: increased hepatic tissue echogenicity; intrahepatic vessel blurring; and echo signal fading. Hepatic steatosis intensity was evaluated with a semi-quantitative method developed by Hamaguchi M. (2007), according to which each of the above steatosis parameters was scored as follows: liver brightness — 0 to 3 points; echo signal fading — 0 to 2 points; vessel blurring — 0 to 1 point [17]. The highest score was six points.

All subjects underwent laboratory tests for total cholesterol, high density and low density lipoprotein cholesterol, triglycerides, creatinine level, and glomerular filtration rate was calculated using the CKD-EPI formula (2011).

All subjects were interviewed; their standard anthropometric parameters (height, wight, body mass index (BMI), and waist circumference) were measured. The obesity type (metabolically healthy/unhealthy phenotype) was determined separately [18,19].

The characteristics of subjects is presented in Table 1.

The data were analysed using MedCalc (version 20.110) and IBM SPSS Statistics (version 18). Qualitative variables were described with absolute and relative frequency (percents). Quantitative variables were described with the median (Me), and the interquartile interval [25th percentile; 75th percentile] was stated. Spearman analysis was used in order to identify correlations bewteen parameters; and a the coefficient of rank correlation was calculated. The value of the coefficient of correlation was interpreted as follows: $r \geq 0.7$ — strong correlation between parameters; $0.3 < r < 0.7$ — moderate correlation between parameters; $r \leq 0.3$ — weak correlation between parameters [20]. The relevance of differences between the groups was evaluated using Mann-Whitney test. Differences were statistically significant if the relevance threshold was 0.05. Variables interdependence was evaluated using logistic regression. ROC-analysis was performed in order to identify the thresholds of test parameters and to determine sensitivity and specificity.

Results

A majority of patients had various cardiovascular risks. Over a half of all patients had abdominal obesity; one out of five patients (21.7 %) was a smoker. A combination of carotid atherosclerosis and arterial atherosclerosis of lower limbs was observed in 76 (43.4 %) patients. The median Hamaguchi score for hepatic steatosis intensity was 2 points (refere to Table 1).

The correlation analysis demonstrated a positive correlation between Hamaguchi score and triglycerides concentration (r=0.317; p=0,0001) and weak negative correlation with high density lipoprotein concentration (r=-0.191; p=0.012).

The group of patients with a combination of carotid atherosclerosis and arterial atherosclerosis of lower limbs

demonstrated a higher Hamaguchi score vs. patients without peripherial atherosclerosis (median Hamaguchi score is 3.0 (0,0; 4.0) points and 1.0 (0.0; 4.0) point, respectively, p=0.026).

In order to identify the potential diagnostic value and optimal Hamaguchi score thresholds for forecasting a combination of carotid stenosis and arterial stenosis of lower limbs, logistic regression analysis and ROC analysis were performed (Table 2, Figure 1).

The logistic regression analysis showed that an increase in Hamaguchi score by one point was associated with 1.192-fold increase in the relative risk of a combined atherosclerosis of both areas (carotid arteries and lower limb arteries) (95 % CI 1.023–1.387).

According to ROC-analysis, an increase in Hamaguchi score by > 2 points made it possible to diagnose a combination of carotid stenosis and arterial stenosis of lower limbs with the sensitivity of 52.6 % and specificity of 63.6 % (AUC=0.596; p=0.024).

In the comparative analysis of Hamaguchi score for men and women, men had statistically higher score vs. women (median score value: 3.0 (1.0; 4.0) points and

Table 1. *Characteristics of patients included in the study*

Показатель/ Indicator	Пациенты / Patients (n=175)	Мужчины/ Men (n=72)	Женщины/ Women (n=103)
Age, years, Me (IQR)	50,0 (44,0; 56,0)	47,5 (44,0; 55,0)	51,0 (45,0; 56,0)
BMI, kg/m^2, Me (IQR)	26,8 (23,4; 30,5)	28,1 (25,7; 31,2)	25,5 (22,3; 29,4)
Obesity: Metabolically healthy phenotype Metabolically unhealthy phenotype	48 (27,4 %) 8 (4,57 %) 40 (22,9 %)	25 (34,7 %) 3 (4,17 %) 22 (31,4 %)	23 (22,3 %) 5 (4,85 %) 18 (17,5 %)
Waist circumference, cm, Me (IQR)	84 (77; 98)	96,0 (85,0; 104)	81,0 (76,0; 91,0)
Abdominal obesity, n (%)	98 (56 %)	49 (68,1 %)	49 (47,6 %)
Smoking, n (%)	38 (21,7 %)	23 (31,9 %)	15 (14,6 %)
Coronary artery disease, n (%)	4 (2,28 %)	4 (5,55 %)	0
Arterial hypertension, n (%)	62 (35,4 %)	36 (50,0 %)	26 (25,2 %)
Type 2 diabetes mellitus, n (%)	3 (1,71 %)	2 (2,78 %)	1 (0,97 %)
Carotid atherosclerosis, n (%)/	121 (69,1 %)	57 (79,2 %)	64 (62,1 %)
Maximum stenosis of the carotid arteries, %, Me (IQR)	24,0 (0,0; 30,0)	26,0 (20,0; 33,8)	20,0 (0,0; 25,0)
Carotid artery stenoses ≥50 %, n (%)	5 (2,86 %)	3 (4,16 %)	2 (1,94 %)
Atherosclerosis of lower limb arteries, n (%)	96 (54,8 %)	54 (75,0 %)	42 (40,8 %)
Lower limb arterial stenoses ≥50 %, n (%)	1 (0,57 %)	1 (1,39 %)	0
Combination of atherosclerosis of carotid arteries and lower extremity arteries, n (%)	76 (43,4 %)	46 (63,9 %)	30 (29,1 %)
Total cholesterol, mmol/l, Me (IQR)	5,91 (5,03; 6,58)	5,74 (4,70; 6,50)	6,06 (5,23; 6,62)
LDL cholesterol, mmol/l, Me (IQR)	3,71 (2,94; 4,55)	3,48 (2,89; 4,36)	3,94 (3,14; 4,59)
HDL cholesterol, mmol/l, Me (IQR)	1,40 (1,16; 1,63)	1,19 (1,01; 1,40)	1,53 (1,35; 1,72)
Triglycerides, mmol/l, Me (IQR)	1,16 (0,80; 1,70)	1,30 (0,90; 2,10)	1,1 (0,80; 1,50)
Creatinine, μmol/l	89,7 (73,5;103;6)	95,8 (81,7; 110)	85,1 (68,9; 100)
pGFR, ml/min/1,73 m^2 to CKD-EPI (2011)	76,0 (63; 91)	78,0 (67,2; 95,3)	70,0 (60,0; 89,0)
Hamaguchi score, Me (IQR)	2,0 (0,0; 4,0)	3,0 (1,0; 4,0)	1,0 (0,0; 4,0)

Note: Me — median; IQR — interquartile range; TCH — total cholesterol; TG — triglycerides; HDL — high-density lipoprotein cholesterol; LDL — low-density lipoprotein cholesterol; cGFR — calculated glomerular filtration rate

Table 2. *Data from the logistic regression analysis*

	B	RMSE	Wald	DF	Significance level	Exp (B)	95 % CI EXP(B)	
							Lower	Upper
HamaScore	0,175	0,077568	5,104	1	0,024	1,192	1,023	1,387
Constant	-0,652	0,232698	7,841	1	0,005	0,521		

Примечание: RMSE — среднеквадратичная ошибка; DF — degrees of freedom
Note: RMSE — Root Mean Square Error; CI — confidence interval

1.0 (0.0; 4.0) points, respectively, p=0.003). However, ROC-analysis results for the assessment of diagnostic value of Hamaguchi score in forecasting a combination of carotid stenosis and arterial atherosclerosis of lower limbs performed separately for men and women did not reveal any statistical significance (Figure 2A–B).

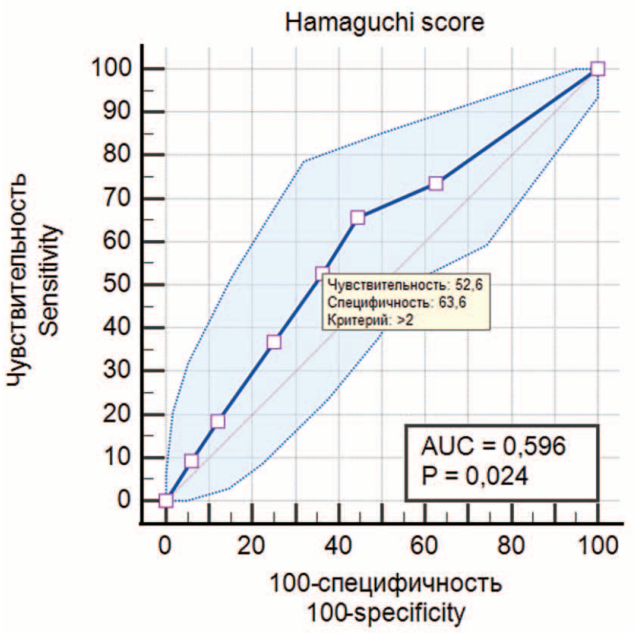

Figure 1. *Results of the ROC analysis for the Hamaguchi scale*

Discussion

Correlation between NAFLD and cardiovascular diseases is one of the most actively studied areas of medicine [21]. NAFLD deaths are caused mostly by cardiovascular events rather than by hepatic outcomes. Also, NAFLD and CVD share a lot of pathogenic mechanisms: system inflammation, insulin resistance, endothelial dysfunction, intestinal dysbiosis [22, 23].

In our study, steatometry Hamaguchi score demonstrated diagnostic value in relation to carotid atherosclerosis and arterial atherosclerosis of lower limbs in patients with NAFLD. Despite the low sensitivity and specificity, we managed to demonstrate for the first time that this ultrasound scale can be a useful tool for the assessment of hepatic steatosis severity and a predictor of a combination of carotid atherosclerosis and arterial atherosclerosis of lower limbs.

In this article, we noted the correlation between Hamaguchi score and lipid metabolism parameters. The available data correlate with the results of previous studies. Sookoian S et al. (2008) demonstrated that carotid atherosclerosis is observed statistically more frequent in patients with NAFLD and noted the correlation between the carotid Intima-media thickness and alanine aminotransferase and gamma-glutamyl transpeptidase levels [24]. The results of a metaanalysis by Tang ASP et al. (2022) showed that the presence of NAFLD increases the chances of carotid atherosclerosis by 3.2 times (95 % CI 2.37–4.32; p<0.0001), while the risk of stroke increases 1.88-fold (95 % CI 1.23–2.88; p=0.02) [25].

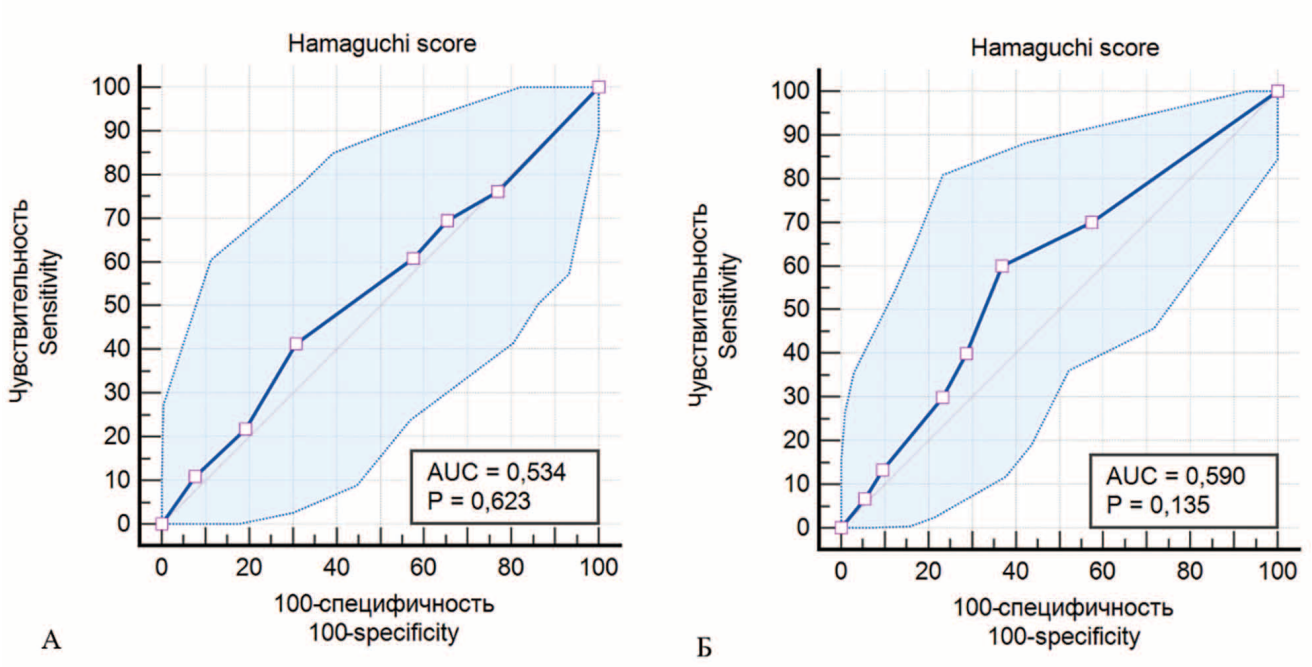

Figure 2. *ROC analysis results for the Hamaguchi scale in men (A) and women (Б)*

A number of studies discuss the correlation between noninvasive markers of hepatic steatosis (in particular, Liver Fat Score (LFS)) and carotid atherosclerosis prevalence, correlations between steatometry indices (Hamaguchi score) and insuline resistance biomarkers (HOMA index) [26, 27].

Conclusion

For NAFLD patients, Hamaguchi score of > 2 points allows diagnosing a combination of carotid stenosis and arterial stenosis of lower limbs with the sensitivity of 52.6 % and specificity of 63.6 %. Evaluation of hepatic steatosis using Hamaguchi method can be used as a screening for peripheral atherosclerosis in high-risk patients.

Вклад авторов

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All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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