Comparative diagnostic value of contrast-enhanced ultrasonography, computed tomography, and magnetic resonance imaging in diagnosis of hepatic hemangiomas

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Summary. *Aim. To compare the value of intravenous contrast-enhanced ultrasonography (US), intravenous contrast-enhanced computed tomography (CT), and magnetic resonance imaging (MRI) in the diagnosis of hepatic hemangiomas.*

Material and methods. The study enrolled 48 patients, aged between 20 and 79 years (35 [72.9%] women, 13 [27.1%] men; mean age, 53.5±12.855 years), who were examined and treated in the Departments of Gastroenterology, Surgery, and Oncology, Hospital of Kaunas University of Medicine, in the year 2007. All patients underwent intravenous contrast-enhanced US, intravenous contrast-enhanced CT, and MRI and were diagnosed with hepatic hemangioma according to the findings of these examinations.

Results. The size of hemangiomas was ⩽2.0 cm in 20 cases (41.7%) and >2.0 cm in 28 (58.3%). No association between hepatic hemangioma and patient's age was found (χ^2=0.547, df=2, P=0.761).

Nearly one-third of hemangiomas were located in the segment IV of the left hepatic lobe. There were a few complicated hemangiomas in the study sample: 2 with calcification and 1 with necrosis.

The sensitivity of CT in the diagnosis of hepatic hemangioma was 76.92%; specificity, 33.3%; positive prognostic value, 83.3%; and negative prognostic value, 25.0%. The sensitivity of intravenous contrast-enhanced US in the diagnosis of hepatic hemangioma was 77.8%; specificity, 100%; positive prognostic value, 100%; and negative prognostic value, 23.1%.

Conclusions. Intravenous contrast-enhanced US is more specific than intravenous contrast-enhanced CT in the diagnosis of hepatic hemangioma (P=0.0005) and has a higher positive prognostic value (P=0.001).

Introduction

Hepatic hemangioma is the second most common benign hepatic lesion after hepatic cysts (1), accounting for 0.4–20% of all hepatic tumors (1–3). Up to 7% of hemangiomas are found in autopsy (1). Generally, it is a solitary, well-defined, and vascularized lesion. In approximately 20–50% of cases, hepatic hemangiomas are multiple.

Complex and controversial data on radiological diagnostics of atypical hemangiomas are reported. It is important to note that manifestation of atypical hemangiomas varies a lot, and this may lead to diagnostic mistakes.

On ultrasonography (US) examination, atypical hemangiomas quite commonly manifest as lesions with an echogenic rim. Large, heterogeneous hemangiomas, rapidly filling hemangiomas, hemangiomas with calcifications, hyalinations, fluid-fluid surface, cystic or lobular hemangiomas, or hemangiomas on pedicles are observed less frequently.

Multiple hemangiomas, hemangiomatosis, focal nodular hyperplasia, and angiosarcoma are quite common lesions associated with hepatic hemangiomas.

Atypical hemangiomas may develop from a growing typical hemangioma or hemangiomas that emerge during gestation.

Likely complications of hemangiomas are the following: inflammation, Kasabach-Merritt syndrome, internal bleeding into hemangioma, hemoperitoneum and compression of surrounding structures. In some cases (i.e., large heterogeneous hemangiomas, hemangiomas with calcifications, hemangiomas on pedicles, or hemangiomas in steatotic liver), magnetic resonanse imaging (MRI) examination is necessary to establish the diagnosis of hemangioma.

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It is reported that hepatic hemangiomas can be diagnosed using liver scintigraphy with ^{99m}Tc-marked red blood cells (4–6). Dynamic liver scintigraphy, performed right after the injection of radioindicator, is followed by static scintigraphy or single-photon emission computed tomography (SPECT). On scintigraphic images, hemangioma is observed as a focus of normal or reduced radioindicator accumulation in the early phases of the examination (2–5 minutes after the radioindicator injection) and as a focus of intensive radioindicator accumulation in the late phases of the examination (1–2 hours after the radioindicator injection) (4–6). It is recommended to perform SPECT if hemangioma is smaller than 2 cm or multiple hemangiomas are suspected. Scintigraphic examination is always carried out after US or (and) computed tomography (CT) that help to estimate location, size, and number of the suspected hemangiomas.

The aim of this study was to compare the value of intravenous contrast-enhanced US, intravenous contrast-enhanced CT, and MRI in the diagnosis of hepatic hemangiomas.

Material and methods
The study enrolled 48 patients, aged between 20 and 79 years (35 [72.9%] women, 13 [27.1%] men; mean age, 53.5±12.855 years), who were investigated and treated in the Departments of Gastroenterology, Surgery, and Oncology, Hospital of Kaunas University of Medicine, in the year 2007. All patients underwent intravenous contrast-enhanced US, intravenous contrast-enhanced CT, and MRI examinations, and the diagnosis of hepatic hemangioma was based on their findings.

Conventional US liver examination (main linear imaging) was performed to assess the ultrasonographic features, location, number, and size of hepatic lesions. An injection of 5 mL contrast agent SonoVue (Bracco, SpA) bolus into the forearm vein (in 2–3 seconds) was followed by 5 mL of physiological solution intravenously. On the contrast-enhanced US examination, the acoustic capacity output was adjusted to mechanical index (MI) 0.1 according to the depth of the lesion and bodily proportions of the patient. The signal of blood flow was enhanced after the injection of contrast agent and registered at the time of peak enhancement (in 30 seconds, 45 seconds, 70 seconds, and more than 2 minutes).

Precontrast and contrast-enhanced CT scanning of the liver was performed using a multisectional (16 sections) spiral CT device (GE Light Speed Pro). Patients were asked to lie down on their back with arms raised above their head. Nonionic contrast agents containing 300 mg of iodine were used intravenously (amount, 100 mL; rate of injection, 3.5 mL/s). Phases of contrast-enhancement were chosen according to the standard protocol of hepatic hemangioma testing (CT scans made in 30, 50, 70 seconds, and 10 minutes after the initiation of intravenous contrast enhancement).

MRI was performed according to the standard protocol of liver testing. Additionally, prolonged T2-weighted sequences were made; their sensitivity in the diagnosis of hepatic hemangioma is reported to be up to 95–98% (2).

The data analysis included patient's age, gender, number of hepatic hemangiomas (patients with ≤3 hemangiomas were selected), segmental location and echogenicity of hepatic foci, contrast agent accumulation in arterial, portal, and venous phases of contrast-enhancement on US and CT examinations, homogenicity of hemangioma, calcification and necrosis of the lesion.

Statistical analysis was performed using statistical package SPSS 14.0 and Microsoft Excel 5.0.

Means of more than two groups were compared using dispersive analysis (ANOVA) with multiple paired comparisons (post hoc Bonferroni criterion). Shapiro-Wilk test was applied to check the normality of distribution of the study sample. Friedman test was used for the statistical comparison of multiple dependent samples, and the relationship between qualitative features was established using χ^2 criterion. The level of significance was $P<0.05$.

The reliability of radiological diagnostics of hepatic hemangiomas was estimated in this study. The sensitivity and specificity, positive and negative prognostic values of contrast-enhanced US and CT examinations for the diagnosis of hepatic hemangioma were calculated and compared using probability comparison test.

Results
The study sample consisted of 35 (72.9%) women and 13 (27.1%) men, aged between 22 and 79 years (mean age, 53.5±12.855).

Shapiro-Wilk test showed that the study population had normal (Gaussian) distribution ($df=48$, $P=0.760$).

A total of 48 hepatic hemangiomas were investigated. Lesions were divided into the groups according to their size at 10-mm intervals. Hemangiomas smaller than 2 cm are diagnostically more important as they tend to be atypical and their diagnostics is more challenging. In nearly half of the cases, hemangiomas were ≤2.0 cm in size (n=20; 41.7%) and larger in 28 (58.3%) cases.

In nearly one-third of cases (n=14; 29.2%), hemangiomas were located in the segment IV of the left hepatic lobe. Most authors also report the fourth hepatic segment as the most common location of focal hepatic lesions; however, reasons for this were not analyzed and remain unknown (7).

Dispersive analysis (ANOVA) of the data showed that the distribution of hemangiomas is homogeneous in different sise groups (Table 1).

Dispersive analysis (ANOVA) with multiple paired comparisons (post hoc Bonferroni criterion) showed no significant relationship between hemangioma size and patient's age (df=5; P=0.379).

We analyzed if hepatic hemangiomas were related to patient's age and found out that patient's age was not related to hepatic hemangiomas (χ^2=0.547; df=2; P=0.761). Literature shows that hemangiomas are most frequent in patients aged between 50 and 70 years (8).

There were few complicated hemangiomas in the study sample: 2 (4.2%) with calcification and 1 (2.1%) with necrosis.

Ultrasonographic features of hepatic hemangiomas on intravenous contrast-enhanced examination were analyzed separately, and results were compared with CT and MRI characteristics of hemangiomas.

Results of ultrasonographic diagnostics of hepatic hemangioma were analyzed. In the arterial phase of contrast-enhanced US examination, 2 (4.2%) foci were hyperechogenic, 44 (91.7%) foci accumulated contrast agent centripetally, and 2 (4.2%) foci were isoechogenic to the surrounding hepatic parenchyma.

In the portal phase of contrast enhancement, 32 (66.7%) hepatic foci were filled with contrast agent centripetally, 5 (10.4%) foci were hypoechogenic, and 11 (22.9%) isoechogenic. In the venous phase, 43 (89.6%) foci became isoechogenic and 5 (20.4%) hypoechogenic.

Statistical analysis of contrast-enhanced US findings showed a significant difference between the contrast agent accumulation in hemangioma in different phases of contrast enhancement, i.e., specific enhancement in different phases are characteristic for hemangioma (Friedman dependent sample test, P=0.0005) (Fig. 1).

The comparative diagnostic values of radiological examination methods in the diagnosis of

Table 1. Homogenicity of the distribution of hemangiomas in different size groups

Size	Number of patients	Mean age	Standard error	Age minimum	Age maximum
Up to 10 mm	5	63.00±14.950	6.686	39	77
10–20 mm	15	51.00±12.473	3.220	26	79
20–40 mm	17	54.71±13.303	3.226	18	74
41–60 mm	9	50.33±11.011	3.670	35	66
61–80 mm	1	69.00*	–	69	69
>100 mm	1	54.00*	–	54	54
Total	48	53.88±12.855	1.856	18	79

*Homogenicity was not evaluated due to small number of cases.
df=3, P=0.935.
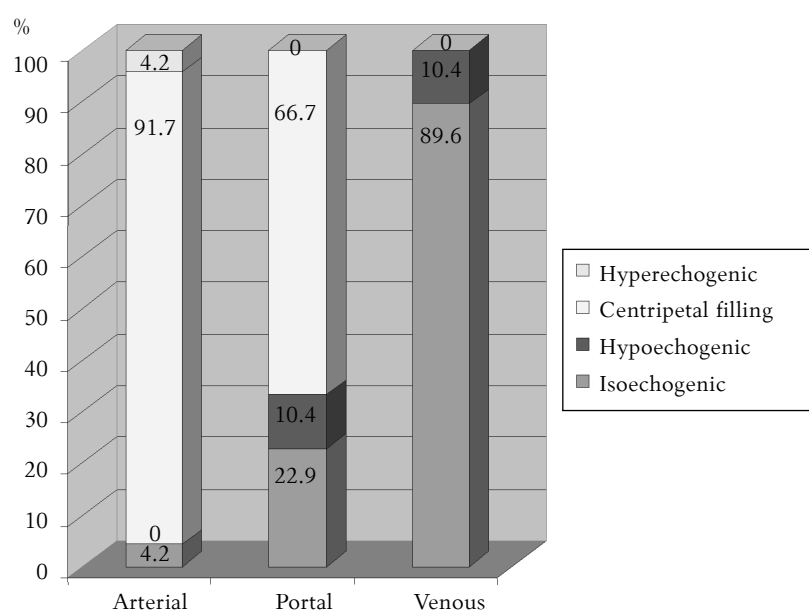

Fig. 1. Type of contrast accumulation in hemangiomas in arterial, portal, and venous phases of contrast enhancement (P=0.0005)

Table 2. Comparison of magnetic resonance imagining (MRI) and intravenous contrast-enhanced computed tomography (CT) findings in the diagnosis of hepatic hemangioma

	MRI positive	MRI negative	Total
CT positive	(a) 30	(b) 6	36
CT negative	(c) 9	(d) 3	12
Total	39	9	48

Sensitivity of CT examination – a probability of positive test results if the disease is present. It is calculated according to the formula: a/a+c (a, number of patients with the disease and positive CT findings; a+c, number of patients with the disease and positive MRI findings).

Specificity of CT examination – a probability of negative test results if the disease is absent. It is calculated according to the formula: d/b+d (d, healthy subjects with negative CT findings; d+b, number of all healthy subjects).

Positive prognostic value of CT examination – a probability of true positive cases. It is calculated according to the formula: a/a+b (a, number of patients with the disease and positive CT findings; a+b, number of all subjects with positive CT findings).

Negative prognostic value of CT examination – a probability of true negative cases. It is calculated according to the formula: d/c+d (d, number of healthy subjects with negative CT findings; c+d, all subjects with negative CT findings).

Table 3. Comparison of magnetic resonance imagining (MRI) and intravenous contrast-enhanced ultrasonography (US) findings in the diagnosis of hepatic hemangioma

	MRI positive	MRI negative	Total
Contrast-enhanced US positive	(a) 35	(b) 0	35
Contrast-enhanced US negative	(c) 10	(d) 3	13
Total	45	3	48

Sensitivity of contrast-enhanced US examination – a probability of positive test results if the disease is present. It is calculated according to the formula: a/a+c (a, number of patients with the disease and positive contrast-enhanced US findings; a+c, number of patients with the disease and positive MRI findings).

Specificity of contrast-enhanced US examination – a probability of negative test results if the disease is absent. It is calculated according to formula: d/b+d (d, healthy subjects with negative contrast-enhanced US findings; d+b, number of all healthy subjects).

Positive prognostic value of contrast-enhanced US examination – a probability of true positive cases. It is calculated according to formula: a/a+b (a, number of patients with the disease and positive contrast-enhanced US findings; a+b, number of all subjects with positive contrast-enhanced US findings).

Negative prognostic value of contrast-enhanced US examination – a probability of true negative cases. It is calculated according to formula: d/c+d (d, number of healthy subjects with negative contrast-enhanced US findings; c+d, all subjects with negative contrast-enhanced US findings).

hemangioma. The diagnostic values of intravenous contrast-enhanced US, CT, and MRI examinations were compared.

The value of MRI and CT examinations in the diagnosis of hepatic hemangioma is presented in Table 2. The sensitivity of CT testing was 76.92%; specificity, 33.3%; positive prognostic value, 83.3%; and negative prognostic value, 25.0%.

Table 3 presents the value of MRI and contrast-enhanced US examinations in the diagnosis of hepatic hemangioma. The sensitivity of intravenous contrast-enhanced US testing was 77.8%; specificity, 100%; positive prognostic value, 100%, and negative prognostic value, 23.1%.

The comparison of diagnostic values of intravenous contrast-enhanced US and intravenous contrast-enhanced CT in the diagnosis of hepatic hemangioma showed that US examination was more specific than CT (P=0.0005) and had a higher positive prognostic value (P=0.001) (Fig. 2).

Discussion

Hemangioma is the most common hepatic lesion, the size of which varies from several millimeters to 20 centimeters. Hemangiomas larger than 10 cm are called gigantic (1, 2). In our study, the size of lesions varied from 0.6 cm to 11.3 cm; 2.1% of them were gigantic.

It is reported that hemangiomas are usually asymptomatic (in 85% of cases) and 5 times more prevalent in women than men (9). This study enrolled more women than men (72.9% and 27.1%,

respectively), but no significant association between hemangioma and gender was found (P>0.05).

Hemangiomas are very rare in cirrhotic liver (8, 10). In our study, none of the patients had this condition.

Conventional US image of hemangioma typically (in 50–60% of cases) demonstrates hyperechogenic and homogeneous well-defined lesion (may be heterogeneous in the center) with or without acoustic enhancement (9, 11–13). In our study, 28 (58.3%) hemangiomas were hyperechogenic and 19 (39.6%) hemangiomas were homogeneous on conventional US examination.

However, ultrasonographic appearance of hemangioma may be atypical and varying on native US images (7, 8, 13–16).

A specific pattern of contrast enhancement of hepatic hemangioma is observed when contrast agent containing sulphur hexafluoride microbubbles is used for the US examination (12, 13, 17). In our study, 88.9% of hemangiomas had typical contrast-enhancement patterns on US examination. Although contrast-enhancement patterns of 11.1% of lesions were malignancy-like, the diagnosis of hepatic hemangioma was confirmed by MRI, which is very specific in this condition (18, 19).
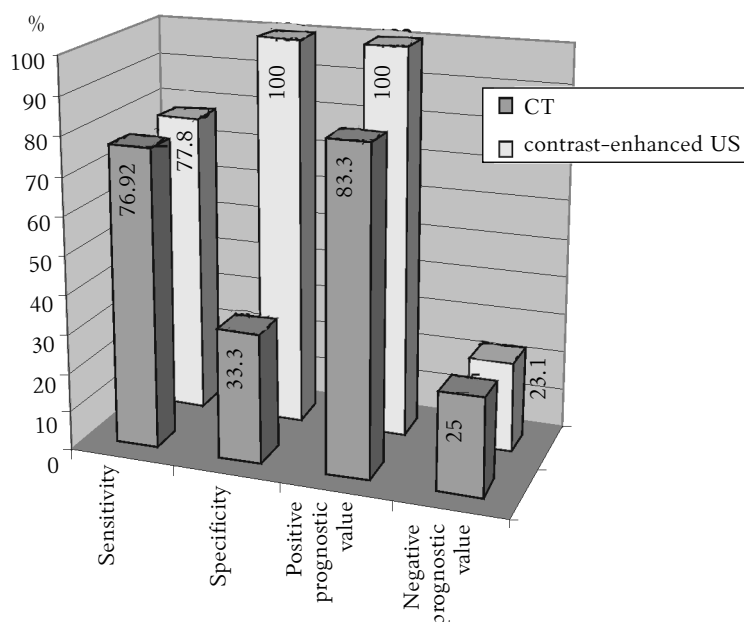
Fig. 2. Comparison of diagnostic values of intravenous bolus contrast-enhanced computed tomography (CT) and intravenous contrast-enhanced ultrasonography (US) in the diagnosis of hepatic hemangioma (significant differences in specificity and positive prognostic value, *P*<0.05).

Atypical radiological features in the venous phase of both contrast-enhanced US and CT complicated the differential diagnosis of hemangiomas from other hepatic lesions, especially hepatocellular carcinoma.

In some cases, no contrast enhancement of hemangioma is noticed on US examination after the injection of microbubbles. This is characteristic of atypical hemangiomas with thrombosis, fibrosclerosis, or hyalination and requires further investigation using CT and MRI (9, 12, 13, 20–22).

On native CT images, hemangiomas appear as hypodense well-defined foci. Calcification is found in 10–20% of cases. A centripetal filling of the lesion is observed on intravenous contrast-enhanced CT 2–15 minutes after the injection of contrast material. An early peripheral contrast accumulation (when contrast is still barely visible in the aorta) is also characteristic of hemangioma. In the early arterial phase of contrast-enhancement, smaller hemangiomas are filled with contrast rapidly and intensively, while large scarred hemangiomas accumulate contrast irregularly and have uncontrasted areas.

In this study, 21 (43.8%) hemangiomas were observed to accumulate contrast centripetally. In the late phases of intravenous contrast-enhancement (after 10 minutes), hemangiomas become isodense to the hepatic parenchyma. We observed 30 (62.5%) isodense lesions in the late phase of contrast enhancement. This sign is one of the most important in the differential diagnosis of hemangioma (10, 20, 23).

All patients underwent intravenous contrast-enhanced US. Hepatic hemangiomas were classified as hyperechogenic, filling centripetally, hypoechogenic, and isoechogenic.

The characteristics of contrast accumulation were evaluated in the arterial, portal, and venous phases of contrast enhancement.

On intravenous contrast-enhanced US examination, all hemangiomas had 1 or 2 typical features that matched the findings of CT or MRI: peripheral accumulation of contrast agent with progressive centripetal filling (88.9%).

The sensitivity of intravenous contrast-enhanced US in the diagnosis of hemangioma was 77.8% and specificity 100%, which was a highly unexpected result.

MRI examination of the liver area plays the most important role in the diagnosis of hemangioma (18). Similarly to hepatic cysts or metastases, most hemangiomas are hypointense on native T1-weighted sequences. On T2-weighted sequences, hyperintense focus with fibrotic areas of low-intensity MRI signal is characteristic of hemangioma. T2-weighted sequences with prolonged relaxation times enable to differentiate hemangiomas from other hepatic lesions (hemangioma is always hyperintense); therefore, contrast-enhanced MRI examination is unnecessary. However, three types of contrast accumulation depending on the size of hemangioma are observed on MRI after intravenous paramagnetic contrast-enhancement with gadolinium agents: a) early filling of the whole focus (small lesions up to 1.5 cm); b) centripetal filling (1.5–5.0-cm lesions); c) centripetal filling when the center of the focus remains hypointense (lesions larger than 5 cm). Centripetal contrast accumulation in the lesion is

the main distinctive sign that helps to differentiate hemangioma from liver metastases (19, 21, 22).

The comparison of diagnostic values of intravenous contrast-enhanced US and intravenous contrast-enhanced CT showed that US examination is more specific than CT examination and has a higher positive prognostic value.

Conclusions

1. Conventional ultrasonography remains the first-choice diagnostic radiological method when focal or diffuse hepatic lesions are suspected.

2. Magnetic resonance imaging is one of the most reliable diagnostic methods in cases of hepatic hemangioma, and histopathologic verification is rarely needed.

3. Contrast-enhanced ultrasonography is more specific than intravenous contrast-enhanced computed tomography ($P=0.0005$) and has a higher positive prognostic value ($P=0.001$).

Kontrastinių ultragarsinio, kompiuterinės tomografijos bei magnetinio rezonanso tomografijos tyrimų lyginamoji vertė kepenų hemangiomų diagnostikoje

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Raktažodžiai: ultragarsinis tyrimas su intraveniniu kontrastavimu, kompiuterinė tomografija, SonoVue, hemangioma, magnetinio rezonanso tomografija.

Santrauka. *Darbo tikslas.* Palyginti ultragarsinio tyrimo (UG) su intraveniniu kontrastavimu, kompiuterinės tomografijos (KT) su kontrastavimu į veną bei magnetinio rezonanso tomografijos (MRT) tyrimo metodų galimybes diagnozuojant kepenų hemangiomas.

Tirtųjų kontingentas ir tyrimo metodai. Tiriamąją grupę sudarė 48 pacientai 2007 m. tirti ir gydyti KMUK Gastroenterologijos, Chirurgijos ir Onkologijos klinikose. Visiems pacientams atlikti UG su kontrastavimu į veną, KT su kontrastavimu į veną bei MRT tyrimai, kurių metu nustatytos hemangiomos kepenyse.

Tiriamųjų amžius – nuo 20 iki 79 metų (72,9 proc.: 35 buvo moterys, 13 vyrų, 27,1 proc., amžiaus vidurkis – 53,5±12,86 metų).

Rezultatai. Tirtoje grupėje beveik pusė hemangiomų, t. y. 20 (41,7 proc.) buvo ≤2,0 cm dydžio, 28 (58,3 proc.) buvo didesnės. Apskaičiavome, jog hemangiomos kepenyse pasireiškia nepriklausomai nuo paciento amžiaus ($\chi^2=0,547$, l.l.s.=2, p=0,761).

Pagal lokalizaciją beveik trečdalis hemangiomų nustatyta kairiosios kepenų skilties ketvirtajame kepenų segmente. Tirtoje grupėje komplikuotų hemangiomų nustatyta nedaug: kalcifikacija nustatyta dviejose hemangiomose, vienoje aptikta nekrozė.

KT tyrimo jautrumas, diagnozuojant kepenų hemangiomas, yra 76,92 proc., specifiškumas – 33,3 proc., teigiama prognostinė vertė – 83,3 proc., neigiama prognostinė vertė – 25,0 proc.

UG su kontrastavimu į veną tyrimo jautrumas, diagnozuojant kepenų hemangiomas, yra 77,8 proc., specifiškumas – 100 proc., teigiama prognostinė vertė – 100 proc., neigiama prognostinė vertė – 23,1 proc.

Išvados. UG tyrimas su kontrastavimu į veną diagnozuojant kepenų hemangiomas, yra specifiškesnis už KT su kontrastavimu į veną (p=0,0005), taip pat didesnė tyrimo teigiama prognostinė vertė (p=0,001).

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