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Prevalence of antibodies to the hepatitis E virus in the population of the Republic of Belarus

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Abstract

Rationale. Hepatitis E (HE) is a zooanthroponosis. Domestic pigs are the main reservoir for hepatitis E virus (HEV) in the Republic of Belarus (RB). Considering the well-developed pig farming, there is a high risk of infection spread among the population; however, the scale of virus circulation and patterns of HE epidemiology in the above region are still insufficiently explored.

The **aim** of the study is to assess HEV seroprevalence specific for the HE epidemic process in RB.

Materials and methods. Serum samples (*n* = 2,784) collected from patients of infectious disease departments at hospitals (*n* = 1,669) and relatively healthy people (*n* = 1,114) from different RB regions were used to measure the activity of alanine aminotransferase (ALT) by a kinetic rate method as well as IgG antibodies to HEV by the enzyme-linked immunosorbent assay (ELISA).

Results. In the group of healthy people, anti-HEV IgG were detected in 7.3% (95% CI, 5.8–9.0). In the group of patients with liver disorders, the detection frequency was significantly higher, reaching 11.2% (95% CI, 9.6–12.9). In the groups of healthy people and patients with elevated ALT levels, the HEV seroprevalence did not depend on their gender or the region of residence. The anti-HEV IgG detection frequency gradually increased among older-age patients and reached the peak levels (15.9% on average) in the over-64 age group.

Conclusions. RB is characterized by intensive HEV circulation, while the HE epidemic process is characterized by a latent nature. The actual prevalence of HE seromarkers among the RB population exceeds the frequency of diagnosed cases, suggesting insufficient vigilance of healthcare workers towards HE and subclinical forms of infection in most of the patients.

Keywords: *hepatitis E, IgG, hepatitis E virus, seroepidemiology*

Ethics approval. The study was conducted with the informed consent of the patients. The research protocol was approved by the Ethics Committee of the Belarusian State Medical University (Protocol 8, April 26, 2016).

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Научная статья
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Распространённость антител к вирусу гепатита Е у населения регионов Республики Беларусь

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Аннотация

Актуальность. Гепатит Е (ГЕ) является зооантропонозом. Основной резервуар вируса гепатита Е (ВГЕ) в Республике Беларусь (РБ) — домашние свиньи, что, в связи с развитой системой свиноводства, предполагает высокий риск распространения инфекции среди населения, однако реальные масштабы циркуляции вируса и закономерности эпидемиологии ГЕ в данном регионе остаются малоизученными.

Цель — изучение серопревалентности ВГЕ, характеризующей эпидемический процесс ГЕ в РБ.

Материалы и методы. В образцах сывороток крови (*n* = 2784), полученных от пациентов инфекционных отделений лечебно-профилактических учреждений (*n* = 1669) и практически здоровых людей (*n* = 1114) из разных регионов РБ, определяли активность аланинаминотрансферазы (АЛТ) кинетическим методом и антитела IgG к ВГЕ методом иммуноферментного анализа.

Результаты. Частота встречаемости анти-ВГЕ IgG в группе условно здоровых людей составила 7,3% (95% ДИ 5,8–9,0). В группе пациентов с поражением печени этот показатель был достоверно выше — 11,2% (95% ДИ 9,6–12,9). Серопревалентность ВГЕ в группах условно здорового населения и пациентов с повышенным уровнем АЛТ не зависела от пола и региона проживания обследуемых лиц. Частота выявления анти-ВГЕ IgG постепенно нарастала по мере увеличения возраста, достигая пиковых значений (в среднем 15,9%) в возрастной группе старше 64 лет.

Выводы. На территории РБ происходит интенсивная циркуляция ВГЕ, при этом эпидемический процесс ГЕ в РБ носит скрытый характер. Реальное распространение серомаркеров ВГЕ среди населения РБ превосходит частоту диагностированных случаев заболевания, что отражает отсутствие настороженности медицинского персонала в отношении ГЕ и указывает на субклиническое течение заболевания у большинства пациентов.

Ключевые слова: *гепатит Е, IgG, вирус гепатита Е, сероэпидемиология*

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Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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Introduction

The hepatitis E virus (HEV) is an RNA-containing virus classified within the *Hepeviridae* family [1] and having pronounced genetic polymorphism [2]. It has been recognized as a major cause of acute viral hepatitis in the world. It has been estimated that approximately 939 million (1 of 8) people have experienced HEV infection worldwide [3]. Five of 8 known HEV genotypes (HEV-1 - HEV-8) can cause infection in humans. Diseases caused by HEV-1 and HEV-2 are anthroponoses; HEV-3 and HEV-4 infect animals, though can also be transmitted to humans; HEV-5 and HEV-6 have been isolated only from wild boars; HEV-7 can infect both humans and dromedaries; HEV-8 has been detected in Bactrian camels, and currently, no viral sequences of HEV-8 have been found in humans. The global spread of HEV is characterized by different epidemiological patterns, which depend on environmental, social, and

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economic factors. Many developing countries are hepatitis E (HE) hyperendemic, especially countries of Southeast Asia and Africa, where the infection presents acute hepatitis that affects primarily young people. Generally, HE is an acute self-limiting disease, which usually resolves on its own, except for infection cases among pregnant women and patients with underlying liver disease, with mortality reaching 25 and 70%, respectively [4].

In countries with poorly developed infrastructure and hot climate, the disease is caused by HEV-1 and HEV-2 transmitted by the fecal-oral route, through contaminated water sources. HE infection occurs both as sporadic cases and as large epidemic outbreaks. Every year, there are approximately 20 million HEV infection cases, including more than 3 million symptomatic cases and 70 thousand HEV-related deaths [5]. Until recently, HE was thought to be of rare occurrence in economically developed regions, being mainly diagnosed in travelers coming back from HE endemic countries. Currently, there is increasing evidence to the contrary [6]. Autochthonous HE infection in developed countries is far more common than previously recognized, and can be more common than hepatitis A [7]. HE mostly affects older men, causing high incidence and mortality rates. The disease has a poor prognosis in the context of pre-existing chronic liver disease, and is frequently misdiagnosed as drug-induced liver injury. Unlike imported infections caused by HEV-1 and HEV-2, autochthonous HE in most developed countries is caused by HEV-3 and is a *zooanthroponotic* infection common among domestic and wild pigs [8]. People can be infected with HEV when eating undercooked pork, raw pork liver, and dry raw sausages or through direct contact with infected animals during their occupational activity, or through pig manure in contaminated settings causing contamination of surface water, viral contamination of crops and virus accumulation in filter-feeding shellfish [9]. Many countries report cases of HEV-3 infection associated with blood transfusion. Chronic HEV-3 infection can develop in immunocompromised people: transplant recipients undergoing immunosuppressive therapy [10], patients with hematological malignancies [11], HIV-infected patients with low CD4 T cell counts [12].

In developed countries, the infection caused by HEV-3 is mostly asymptomatic [14]; however, in patients with chronic liver disease, it can often be complicated by acute liver failure with the death rates reaching 27% [13]. The authors of the study performed in Denmark have found that though HE incidence is critically low, the population demonstrates high prevalence of anamnestic IgG antibodies to HEV, which reaches 20%. This phenomenon of HEV epidemiology is observed in most of the developed countries and is known as the Balayan paradox in Russian literature [15].

The Republic of Belarus (RB) belongs to HE low-prevalence regions [16] with 0.02-0.04 reported cases per 100 thousand population. There is hardly any HE-specific diagnostics at healthcare facilities; therefore, there is no evidence of actual HE prevalence rates in RB. Cases with manifest HE infection are generally diagnosed with other diseases and, most likely, most of them are recorded as hepatitis of unknown etiology. It has been found that in RB, HE is autochthonous and can be imported from other territories [17]. Domestic pigs are the main HEV reservoir in RB [18]. As the HE epidemic process is presumably of latent nature, the assessment of the actual HEV circulation among the population and development of the required epidemic control measures, considering the *zooanthroponotic* nature of the infection, are of high priority to the RB healthcare.

The **aim** of this study was to assess the prevalence of anamnestic IgG antibodies to HEV (anti-HEV IgG) in different groups of population in the Brest and Minsk Regions of RB, depending on the gender and age.

Materials and methods

A total of 2,784 sera samples were tested. All of them were collected from different groups of population residing in the Brest and Minsk Regions of RB. The study participants were people representing 6 age cohorts: under 25 years, 25-34, 35-44, 45-54, 55-64 years, and over 64 years. The profiles of the age cohorts are presented in **Fig. 1**. Each age group included both men and women; the average gender ratio was 1 : 1.13. The gender-age profile of the groups from different regions is presented in **Table 1**.

The study included two categories of people. The first category included relatively healthy people (n = 1,114) with no gastrointestinal tract-related complaints, with liver damage-specific liver enzyme, alanine aminotransferase (ALT) levels within the normal range (< 53 IU/L). The other category (n = 1,669) included patients of infectious disease departments at hospitals; these patients had liver-related complaints, and their ALT levels were more than twice as high as the normal reference level (> 106 IU/L). The design of the study is presented in **Fig. 2**.

The ALT activity in sera was measured with the reagent kit for measuring the activity of aminotransferases (Analiz-X) in accordance with the manufacturer's instructions. Anti-HEV IgG antibodies in serum samples were detected using enzyme-linked immunosorbent assay and the DS-EIA-ANTI-HEV-G reagent kit (RPC Diagnostic Systems), in accordance with the manufacturer's instructions. We also used our own new assay to detect IgG antibodies to HEV in sera based on the indirect solid-phase enzyme-linked immunosorbent assay [14]. Recombinant proteins ORF2 and ORF3 HEV-3, which were developed at the Mechnikov Research Institute of Vaccines and Sera, were used as antigens [19]. All the positive results obtained with our assay were verified through the repeat tests of samples using the reference DS-EIA-ANTI-HEV-G kit.

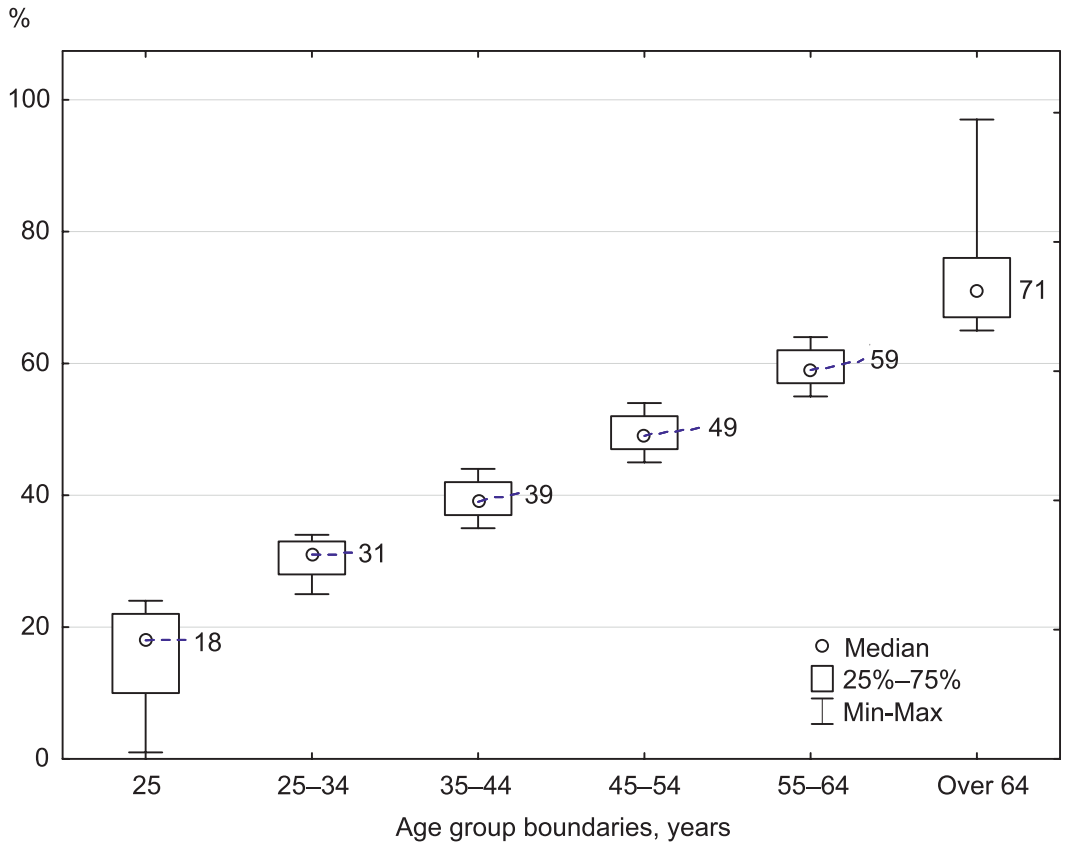

Fig. 1. Age cohort profiles.

The statistical analysis of the obtained results was performed using the Statistica for Windows 12.0 software (StatSoft Inc.). The quantitative variables were expressed as a median (Me) of the upper and lower quartiles (Q_1–Q_3). The resulting data were verified for their conformity to the normal distribution (the Shapiro-Wilk W-test). Nonparametric statistics methods were used, if the conformity was absent. The significance of differences between the groups was assessed with the Mann-Whitney U-test for independent groups. The association between the variables was measured with the correlation coefficient calculated using Spearman's non-parametric test. The qualitative variables were analyzed for absolute frequency (*n*), relative frequency – a percentage (%) of the total number of cases in the studied group, and the 95% confidence interval (95% CI). The significance of differences in percentages was measured with the chi-square (χ^2) test. Differences were considered significant at $p < 0.05$.

Results

Anti-HEV IgG antibodies were detected in 268 of 2,784 serum samples collected from people in two studied groups, amounting to 9.6% (95% CI, 8.5–10.8). In the group of patients with liver disorders, anti-HEV IgG antibodies were detected in 187 of 1,669 tested samples, thus amounting to 11.2% (95% CI, 9.6–12.9). In the group of healthy people, anti-HEV IgG antibodies were detected in 81 of 1,114 tested samples, thus amounting to 7.3% (95 CI, 5.8–9.0). Thus, in the group of patients with liver disorders accompanied by elevated levels of specific transaminases, the detection frequency of anamnestic anti-HEV IgG antibodies was significantly higher than in the group of healthy people ($\chi^2 = 11.842$; $p = 0.00058$; **Fig. 3**).

In both groups, the overall HEV seroprevalence did not depend on the gender (Fig. 3). Among 268 seropositive individuals, 112 were women, thus accounting for 8.6% of total 1,194 participating women (95% CI, 7.2–10.2). Among 1,478 tested serum samples from men, seropositive samples amounted to 156 (10.6%; 95% CI, 9.1–12.2). The differences in detection frequency of anti-HEV IgG antibodies in men and women in both studied groups are not statistically significant ($\chi^2 = 3.121$; $p = 0.07728$). When studying the prevalence of anamnestic antibodies to HEV, we detected anti-HEV IgG antibodies in sera of 43 of 613 women from the group of healthy people (7.0%; 95% CI, 5.1–9.5). Among the women from the group of patients with elevated ALT levels, anti-HEV IgG antibodies were detected in 69 of 693 samples (10.0%; 95% CI, 7.9–12.4). Thus, anti-HEV IgG antibodies in group of women with liver disorders were detected more frequently, with the detection rates close to statistically

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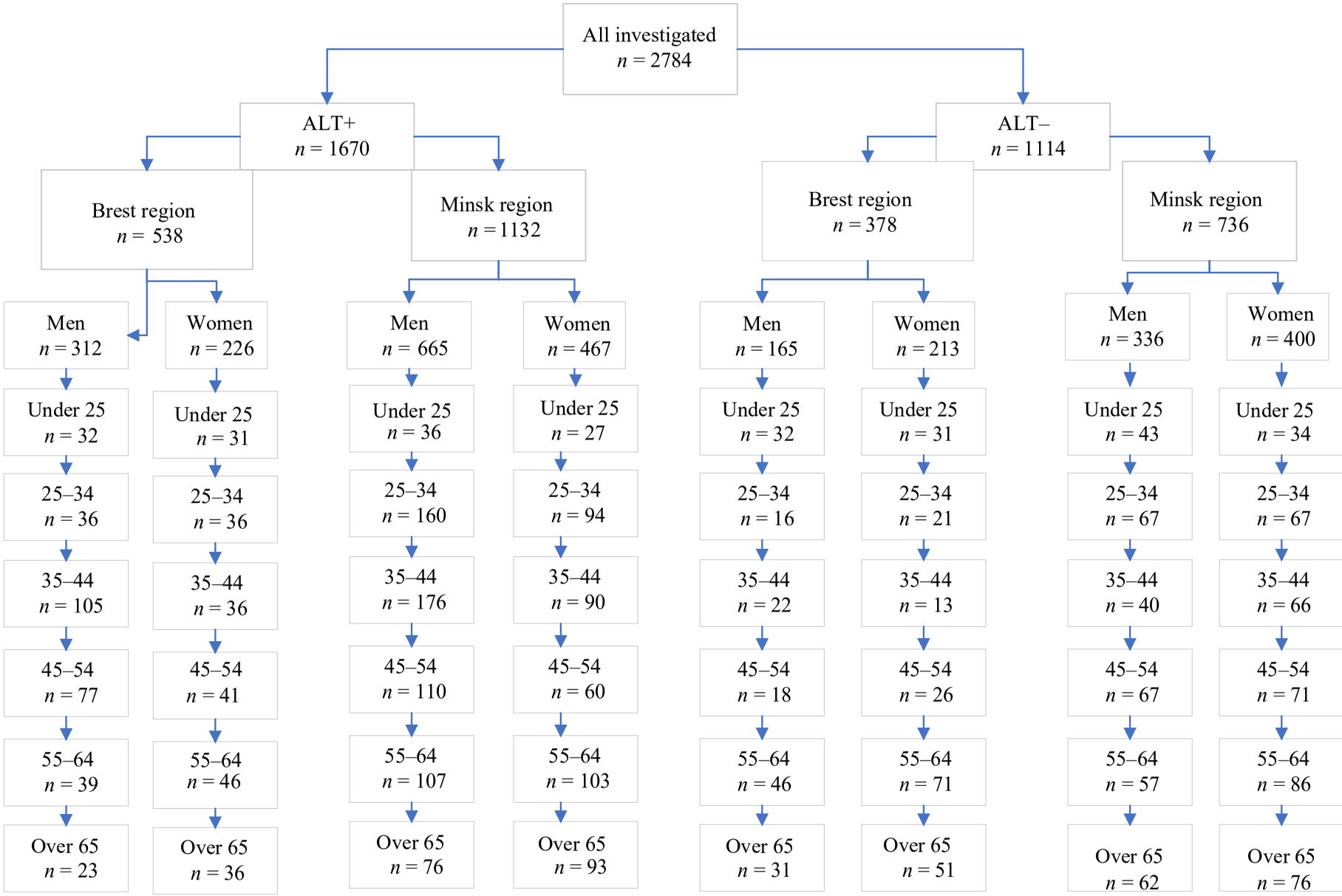

Fig. 2. Study design.

Table 1. Sex and age characteristics of the studied groups

Region	Age category	Sex		Total
		female	male	
Brest region	< 25	62	64	126
	25–34	57	52	109
	35–44	49	127	176
	45–54	67	95	162
	55–64	117	85	202
	> 64	87	54	141
	Total	439	477	916
Minsk region	< 25	61	79	140
	25–34	161	227	388
	35–44	156	216	372
	45–54	131	177	308
	55–64	189	164	353
	> 64	169	138	307
	Total	867	1001	1868
Total		1306	1478	2784

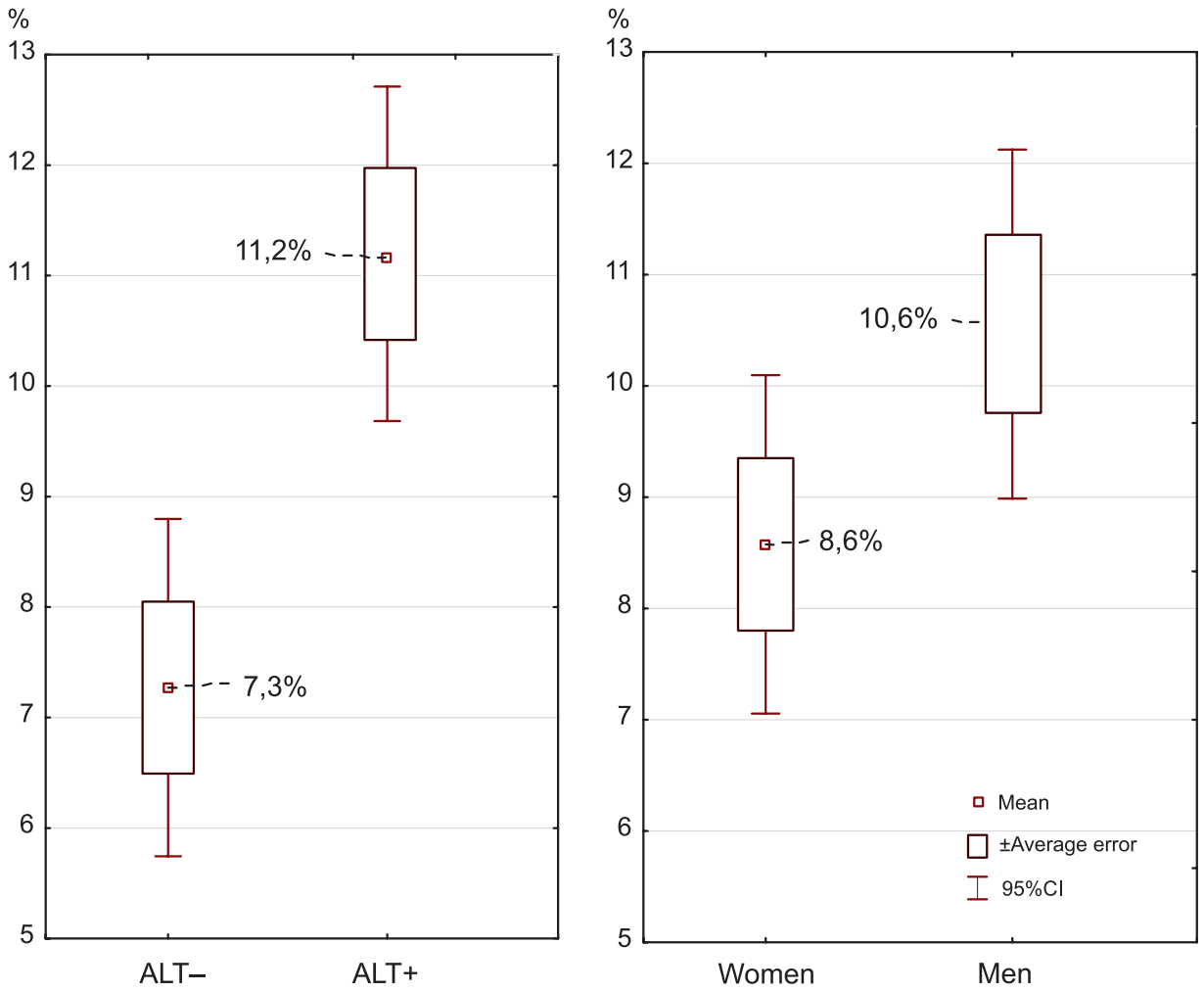

Fig. 3. Detection frequency of anti-HEV IgG in the studied groups.

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significant (χ^2 = 3,591; p = 0.05810). The detection frequency of anamnestic antibodies to HEV among men was different. Anti-HEV IgG antibodies in the samples from the group of healthy people were detected in 38 of 501 samples (7.6%; 95% CI, 5.4–10.4). Among the patients with liver disorders, anti-HEV IgG antibodies were detected in 118 of 977 samples (12.1%; 95% CI, 10.0–14.5), i.e. significantly more frequently than in the group of healthy people (χ^2 = 7.0813; p = 0.0078; **Fig. 4**).

The analysis of the HEV seroprevalence in different regions of RB showed that among residents of the Brest Region, anti-HEV IgG antibodies were detected in 80 samples out of 916 tested samples, thus amounting to 8.7% (95% CI, 6.93–10.87). Among the participants from the Minsk Region, antibodies were detected in 188 samples out of 1,868 tested samples (10.1%; 95% CI, 8.68–11.61). The detection rates for antibodies among the participants representing different RB regions did not demonstrate any statistically significant differences (χ^2 = 1.25; p = 0.263392). Among the healthy women, the detection rate was 6.6% for the Brest Region (14 of 213; 95% CI, 3.6–11.0), for the Minsk Region - 7.3% (29 of 400; 95% CI, 4.9-10.4). Among the healthy male residents of these regions, anti-HEV IgG antibodies were detected at a rate of 7.3% (12 of 165; 95% CI, 3.8–12.7) and 7.7% (26 of 336; 95% CI, 5.1–11.3), respectively (**Fig. 5**).

Among patients with liver disorders, anti-HEV IgG antibodies were detected more frequently; however, no statistically significant differences depending on the region of residence were found. Among the female residents of the Brest Region antibodies were detected at a rate of 8.0% (18 of 226; 95% CI, 4.7–12.6), in the Minsk Region – 10.9% (51 of 467; 95% CI, 8.1–14.4). Among the men, anti-HEV IgG antibodies were detected more frequently, though no significant differences that would depend on the region of residence were found: The detection rate for the Brest Region was 11.5% (36 of 312; 95% CI, 8.1-15.6), for the Minsk Region – 12.3% (82 of 665; 95% CI, 9.8–15.3). Thus, the analysis of the detection rate of antibodies to HEV in different clinical groups, depending on the gender, from the Brest and Minsk Regions did not show any statistically significant differences, thus suggesting that the HE epidemic process has similar patterns in these regions.

The HEV seroprevalence increased with the age of people. The comparison of detection rates of anti-HEV IgG antibodies in people of the neighboring age groups revealed statistically significant differences only in the group of patients with liver disorders (**Fig. 6**).

In the age group over 64 years, antibodies were detected in 46 of 228 patients (20.2%; 95% CI, 14.8–26.9). This rate is significantly higher than in any other age group of patients. For example, in the group of 55-64 years, anti-HEV IgG antibodies were detected significantly more rarely, accounting for 10.8% (32 of 295; 95% CI, 7.4–15.3; χ^2 = 8.82; p = 0.003). In the group of healthy people, significant differences in the anti-HEV

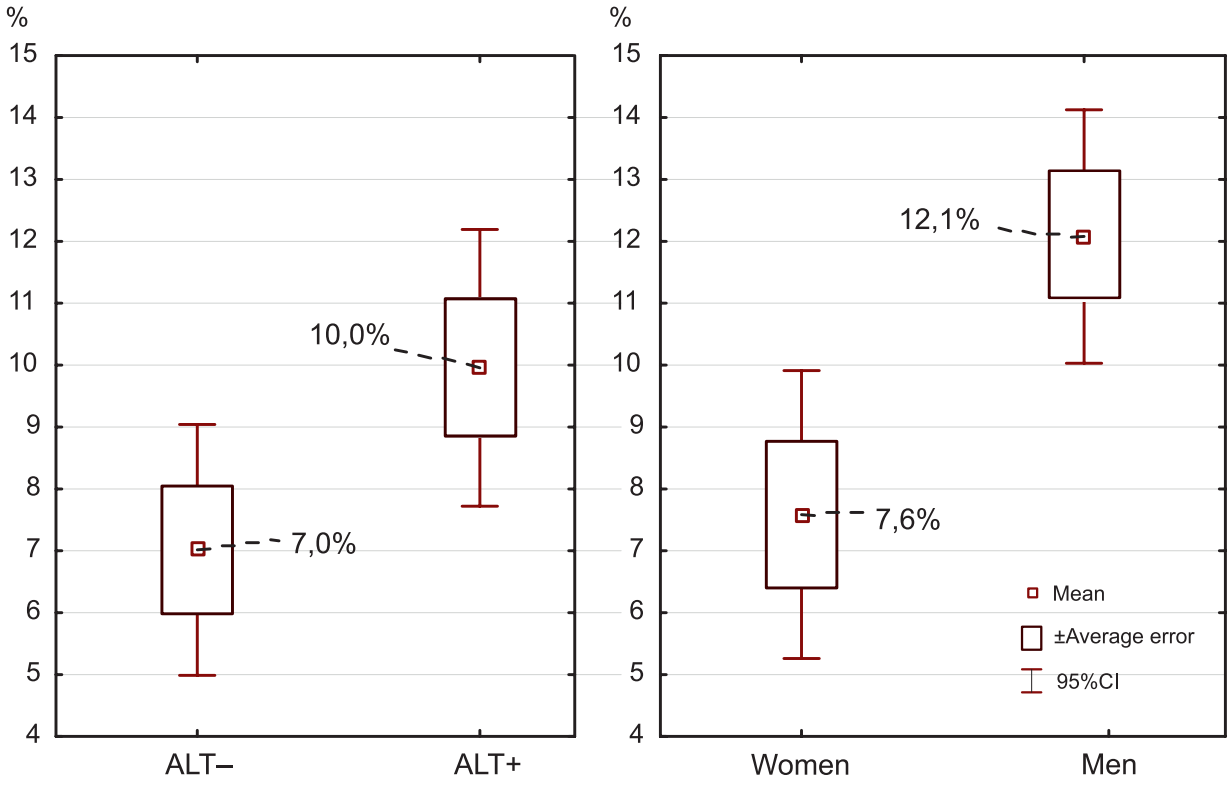

Fig. 4. Detection frequency of anti-HEV IgG in men and women in the studied groups.

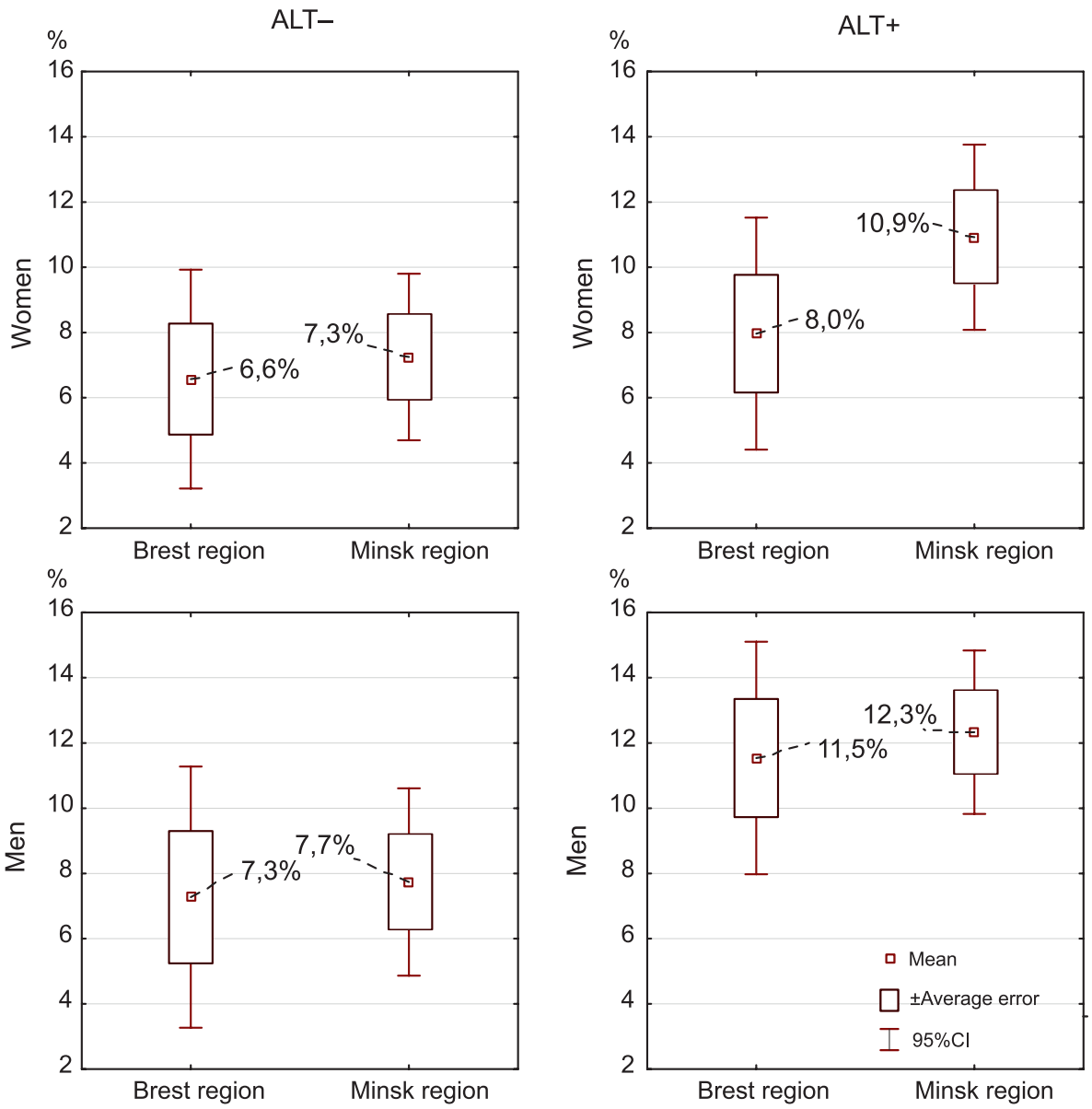

Fig. 5. Detection frequency of anti-HEV IgG among men and women in the studied groups by the region.

IgG antibody detection rates were demonstrated only by two age groups. In the group of 0-24 years, 4 positive sera were detected among 140 tested samples (2.9%; 95% CI, 0.8–7.3). The group over 64 years had 25 of 220 seropositive individuals (11.4%; 95% CI, 7.4–16.8), showing significantly higher detection rates than in the younger group ($\chi^2 = 7.25$; $p = 0.0071$).

Spearman's correlation coefficient was used to find the statistically significant positive association between the detection frequency of anti-HEV IgG antibodies and the increasing age of people. The highest value of the correlation coefficient (n = 977; ρ = 0.124; $p < 0.001$) was demonstrated by the male group with elevated ALT levels (ALT+) (Table 2). The correlation coefficient was calculated through the comparison of detection frequencies of anti-HEV IgG antibodies in the studied groups, depending on the age of the participants.

Discussion

The performed studies have shown that the detection frequency of anamnestic antibodies to HEV in the groups of healthy population of RB is 7.3% on average, thus being significantly lower than the seroprevalence in the population of European countries – 9.3% ($\chi^2 = 5.45$; $p = 0.0196$) [3]. In RB, this rate is comparable with the rates in Italy and Switzerland, accounting for 7.28 and 7.25%, respectively [3]. At the same time, the HEV seroprevalence among healthy residents of RB is significantly lower than in France, Germany, the Netherlands, and Poland, which are HE enclaves in Europe, where anti-HEV IgG seroprevalence ranges from 14.17% to 16.07% [3]. The meta-analysis of literature data shows that in European countries, among patients with acute hepatitis, the frequency of positive detection results for anti-HEV IgG antibodies reaches 21.5% [3].

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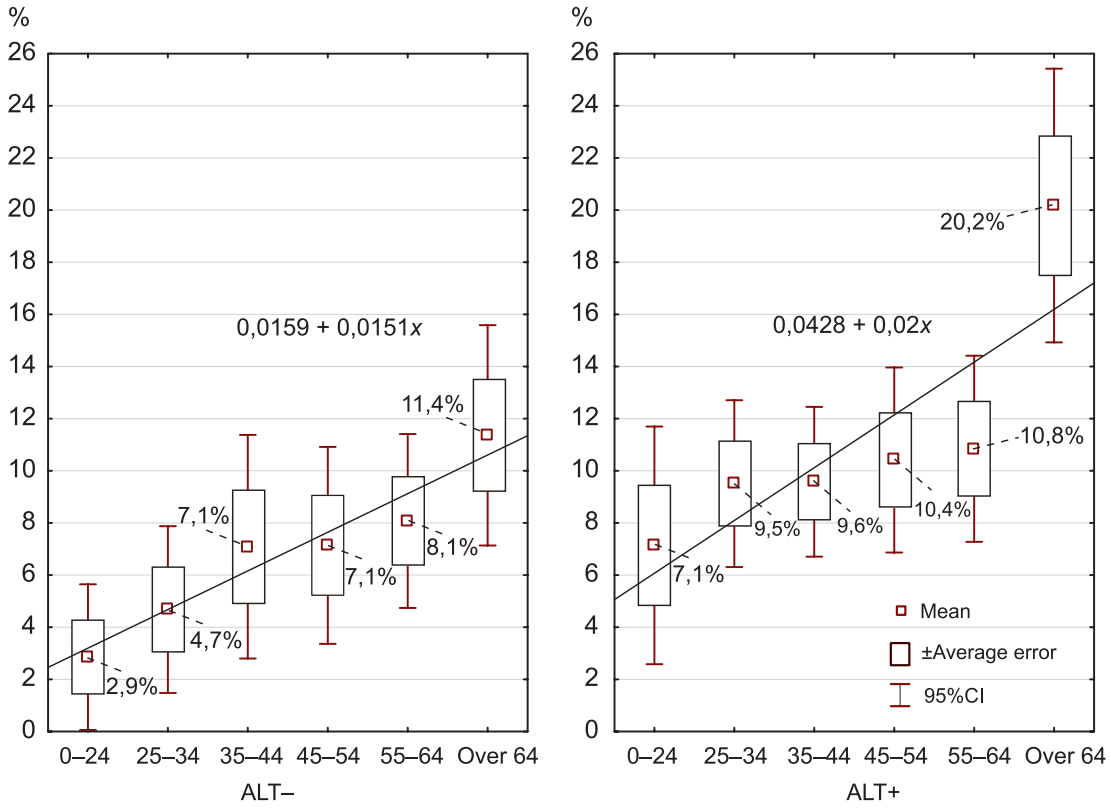

Fig. 6. Detection frequency of anti-HEV IgG in the studied groups, depending on age.

Our studies show that the prevalence of specific antibodies in the group of patients with elevated levels of transaminases is as low as 11.2%, thus implying a less significant role of HEV as a factor of viral hepatitis development in the studied regions of RB. In the meantime, the actual prevalence of HE seromarkers among the population is significantly higher than the number of diagnosed cases, thus being indicative of the latent intensive circulation of HEV. We can confidently assume that the low number of recorded infection cases can be explained by the insufficient vigilance of healthcare workers towards HE and by subclinical forms of infection in most of the patients.

In RB, the detection rate of anti-HEV tends to increase gradually with the age of people, reaching peak levels of 20.2% in the over-64 age group of people with liver damage. This increase can be caused by the long-term, more than 20 years-long persistence of antibodies in humans [20] and by epidemiological, clinical, or pathogenic HE characteristics typical of people of the senior age group. The correlative positive association between the increase in the detection frequency of anti-HEV IgG antibodies and the age of people is statistically significant. The patterns of the retention of antibodies in people and the age-related increasing detection rate require further research.

This study did not find any statistically significant differences in the prevalence of antibodies to HEV, depending on the region of residence, which can be explained by the similar levels of infrastructure devel-

Table 2. Spearman's correlation coefficient (ρ) for the detection frequency of anti-HEV IgG and the age of participants, and its significance

Group	*n*	ρ	*p*
Total number of participants	2784	0,099	< 0,001
ALT+	1670	0,099	< 0,001
Men	1478	0,113	< 0,001
Men ALT+	977	0,124	< 0,001
Men ALT–	501	0,107	< 0,05
Women	1306	0,091	< 0,01
Women ALT+	693	0,080	< 0,05
Women ALT–	613	0,109	< 0,01

opment, similar patterns of occupational activity and lifestyle population as well as by similar patterns of the HE epidemic process in the central and western regions of RB.

The gender of an individual has no statistically significant effect on the prevalence of anti-HEV IgG antibodies, thus suggesting that there are no significant differences in susceptibility of men and women to this infection.

The obtained results highlight the importance of wide-scale specific HEV diagnostics for patients with hepatitis of unknown etiology. Urgent steps should be taken to develop new sanitary and epidemic control measures and to improve the existing programs aimed at prevention of occurrence and spread of HE, considering the *zooanthroponotic* nature of this infection.

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