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# Seroprevalence and risk factors for hepatitis E virus infection in the Romanian adult population: a cross-sectional study in a tertiary hospital

Valeriu Gheorghiță[1*], Ion Ștefan[2], Ioana Diana Olaru[3], Adelina Maria Radu[4], Oana Săndulescu[5], Anca Streinu-Cercel[5], Adrian Streinu-Cercel[5]

*1. "Carol Davila" University of Medicine and Pharmacy; Central Military University Emergency Hospital "Dr. Carol Davila", Bucharest, Romania*
*2. Central Military University Emergency Hospital "Dr. Carol Davila"; "Titu Maiorescu" University, Faculty of Medicine, Bucharest, Romania*
*3. Biomedical Research and Training Institute, Harare, Zimbabwe*
*4. National Institute for Infectious Diseases "Prof. Dr. Matei Balş", Bucharest, Romania*
*5."Carol Davila" University of Medicine and Pharmacy; National Institute for Infectious Diseases "Prof. Dr. Matei Balş", Bucharest, Romania*

## Abstract

***Background:*** *The primary goal was to estimate the seroprevalence of autochthonous hepatitis E virus (HEV) infection in adult Romanian population. Additionally, we aimed to identify the risk factors associated with the HEV seropositive status.* ***Methods****: Between January 2015 and December 2016, 201 adult patients were tested for anti-HEV-IgG. Multivariate logistic regression was used to examine for factors associated with a positive HEV-IgG test. The level of significance was set at α = 0.05.* ***Results****: The final analysis included 175 patients who followed the study protocol. Forty-sex (26.3%) had positive, 121 (69.1%) had negative, and 8 (4.6%) had indeterminate anti-HEV-IgG results. Patients with positive anti-HEV-IgG were older [median age: 54.5 years (IQR 43-65)] compared to patients with negative anti-HEV-IgG [median age: 37.5 years (IQR 28-57.5)], p <0.001. A positive HEV-IgG was more common in patients with history of blood transfusions [n=10 (22.7%) versus (vs) n=11 (9.4%), p=0.025], in those with immunosuppressive conditions [n=18 (40.9%) vs n=27 (23.1%), p=0.025] and in patients with positive hepatitis B surface antigen (HBsAg) [n=14 (31.1%) vs n=10 (10.3%), p=0.002].* ***Conclusions****: In conclusion, we found that autochthonous HEV seropositivity is common in our study population, especially in older patients, previous blood transfusions, presence of immunosuppressive conditions, and positive HBsAg.*

***Keywords:*** *hepatitis E, HEV, risk factors, Romanian population, seroprevalence*

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***Corresponding author**: Valeriu Gheorghita, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania. E-mail: gvaleriu21@yahoo.com

## Introduction

Worldwide, hepatitis E virus (HEV) infection is an important global health problem given the significant morbidity and mortality associated with this infection (1). An estimated 20 million HEV infections occur annually in limited-resource countries with more than 3 million symptomatic cases and up to 60,000 deaths (2). However, HEV continues to be the most neglected of all five types of viral hepatitis (3). HEV, a non-enveloped positive strand RNA virus, belongs to the Hepeviridae family, and comprises eight different genotypes (4). The first two genotypes (gt 1 and 2) infect only humans resulting mainly in waterborne outbreaks in developing countries, whereas gt 3 and 4 infect mammalian animals with occasional cross-species transmission to humans in high-income countries (1,5,6). Historically, HEV infection has been linked to fecal-oral transmission in less developed geographic regions, such as Southeast Asia, Africa and Mexico, where it continues to evolve to a high endemic level (7,8). In the last decade, autochthonous HEV infections have been frequently reported in high-income countries and were largely related to zoonotic transmission, but also to blood transfusions or organ transplant (2,6,9). According to new data on HEV seroprevalence in the general population, it is estimated that at least two million cases are locally acquired each year in Europe, with HEV gt 3 as the dominant circulating genotype (1,8,10,11). HEV infection is generally self-limited, with a high percentage of asymptomatic acute infections. Nevertheless, HEV gt 1 and 2 infections are associated with an increased risk of death in pregnant women and persons with pre-existing chronic liver disease (2,12,13). On the other hand, in severely immunocompromised patients, HEV gt 3 and 4 infections can cause chronic hepatitis with rapid development of liver cirrhosis, and extrahepatic manifestations such as neurological and kidney injury in the context of acute or chronic infections (1,12). Antiviral therapy with pegylated interferon-α, ribavirin or a combination of the two has been shown to be effective in treating chronic hepatitis E and HEV-associated glomerular disease, with sustained virological responses of 85-90% after ribavirin monotherapy (12). Although a promising vaccine for HEV has been developed and licensed in China, the World Health Organization still does not recommend the introduction of the vaccine for routine immunization in populations where epidemic and sporadic hepatitis E is common (13).

Although there have been reports of autochthonous cases of acute HEV infection, robust information about the seroprevalence of HEV infection in the Romanian population has not yet been published. Thus, our main goal was to estimate the seroprevalence of HEV infection in the adult population from a limited geographical area of Romania. We also aimed to identify the risk factors associated with the presence of anti-HEV IgG antibodies in order to develop a strategy to limit transmission of HEV in the general population, and in particular to the subset of patients at increased risk of developing chronic infection.

## Methods

### *Study Design and Populations*

We conducted a cross-sectional study in the National Institute for Infectious Diseases "Prof Dr Matei Bals" from Bucharest, Romania, between January 2015 and December 2016. The population served by this hospital comes mainly from the south-eastern part of Romania, with over 100,000 adult and pediatric patients presenting to the hospital annually.

We included adult patients, aged over 18 years. The study population was randomly selected from the target population that was represented by the patients who were admitted for any medi-

cal reason to various departments of the institute, including emergency room.

Enrollment was performed over a period of 24 months, in order to increase the chance to get higher number of patients and to include a more diverse population with the highest territorial coverage. Patients were invited to participate in the study within the first 24 hours of admission after they have been selected randomly by the electronic system of the hospital taking into account the registration number assigned to each patient at the moment of presentation to the hospital. More than 90% of patients who were invited to participate in the study consented.

To evaluate the risk factors associated with HEV infection, all patients included in the study completed an epidemiological questionnaire consisting of demographic data, pregnant status for women, residence, activities involving contact with wild, farm or household animals, history of travel abroad during the previous year, dietary habits including consumption of undercooked or raw meat products and sea food, drinking of water from unsafe sources, co-infection with hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV), history of blood or blood product transfusions and the presence of other conditions of immunosuppression such as malignancies, patients with solid organ transplantation and debilitating chronic diseases (diabetes, cirrhosis).

### *Ethics*

The study was approved by the Ethics Committee of the hospital and was conducted in accordance with the ethical principles of the latest version of the 2013 Helsinki Declaration. All patients signed the informed consent before enrolling in the study cohort.

### *Laboratory method for HEV testing*

Serum samples were tested for anti-HEV IgG using the anti-HEV IgG enzyme-linked immunosorbent assay (ELISA) kit (MP Diagnostics HEV ELISA, MP Biomedicals). The test and interpretation of the results were performed according to the manufacturer's instructions. The results were finally reported as positive, indeterminate or negative for presence of anti-HEV IgG.

### *Statistical Analysis*

Statistical analysis was performed using STATA version 14 (Stata-Corp, TX, USA). The $\chi^2$ test was used to evaluate for differences between groups for categorical variables. For continuous variables, the Mann-Whitney U-test was used. Multivariate logistic regression was used to examine for factors associated with a positive anti-HEV IgG test. Data were represented by descriptive statistics as medians, interquartile range (IQR), 95% confidence intervals (CIs), and total and relative frequencies. The level of significance was set at $\alpha = 0.05$.

## Results

The study included 175 patients, of which 46 (26.3%) had a positive, 121 (69.1%) had a negative, and 8 (4.6%) had an indeterminate anti-HEV IgG result. We excluded from the final statistical analysis those individuals with indeterminate anti-HEV IgG results. The baseline characteristics of the study population are presented in Table 1.

Regarding the age distribution, based on the presence or absence of the serum anti-HEV IgG in the study group, our analysis showed that patients with positive anti-HEV IgG were older [median age of 54.5 years (IQR 43-65)] than patients with negative anti-HEV IgG [median age of 37.5 years (IQR 28-57.5)], $p < 0.001$ (Figure 1).

A positive HEV serology was more common in patients with a history of blood transfusions [n=10 (22.7%) versus (vs) n=11 (9.4%), p=0.025], in those with immunosuppressive conditions [n=18 (40.9%) vs n=27 (23.1%), p=0.025] and in patients with positive hepatitis B surface an-

**Table 1. Characteristics of patients according to the anti-HEV IgG result by univariate analysis**

| Characteristic | Total† N=167 | anti-HEV IgG negative N=121 | anti-HEV IgG positive N=46 | p-value |
|---|---|---|---|---|
| Age, median (IQR) | 45 (31-63) | 37.5 (28-57.5) | 54.5 (43-65) | **<0.001** |
| Male sex, n (%) | 61 (37.4) | 41 (35.0) | 20 (43.5) | 0.317 |
| Pregnant, n (%) | 12 (7.3) | 12 (10.2) | 0 (0) | 0.025 |
| Rural residence, n (%) | 38 (23.5) | 28 (23.7) | 10 (22.7) | 0.894 |
| Contact with animals, n (%) | 47 (29.0) | 35 (29.7) | 12 (27.3) | 0.766 |
| Contact with farm animals, n (%) | 2 (1.2) | 1 (0.9) | 1 (2.3) | 0.465 |
| Contact with animals within household, n (%) | 47 (29.0) | 35 (29.7) | 12 (27.3) | 0.766 |
| Pigs, n (%) | 36 (22.2) | 28 (23.7) | 8 (18.2) | 0.450 |
| Cattle, n (%) | 13 (8.0) | 11 (9.3) | 2 (4.6) | 0.320 |
| Goats, n (%) | 5 (3.1) | 3 (2.5) | 2 (4.6) | 0.512 |
| Sheep, n (%) | 7 (4.3) | 3 (2.5) | 4 (9.1) | 0.068 |
| Horses, n (%) | 3 (1.9) | 1 (0.9) | 2 (4.6) | 0.120 |
| Poultry, n (%) | 20 (12.4) | 14 (11.9) | 6 (13.6) | 0.760 |
| Hunter, n (%) | 4 (2.5) | 1 (0.85) | 3 (6.8) | **0.029** |
| IVDU, n (%) | 2 (1.2) | 2 (1.7) | 0 (0) | 0.385 |
| Transfusion of blood or blood products, n (%) | 21 (13.0) | 11 (9.4) | 10 (22.7) | **0.025** |
| Travel abroad within the last year, n (%) | 76 (46.9) | 60 (50.9) | 16 (36.4) | 0.100 |
| Consumption of undercooked meat, n (%) | 87 (53.7) | 64 (54.2) | 23 (52.3) | 0.823 |
| Consumption of animal organs, n (%) | 65 (40.1) | 43 (36.4) | 22 (50.0) | 0.117 |
| Consumption of raw/ undercooked seafood, n (%) | 38 (23.5) | 29 (24.6) | 9 (20.5) | 0.582 |
| Unsafe water source, n (%) | 48 (29.6) | 34 (28.8) | 14 (31.8) | 0.710 |
| Immunosuppressive condition, n (%) | 45 (28.0) | 27 (23.1) | 18 (40.9) | **0.025** |
| Immunosuppressive treatment, n (%) | 11 (6.8) | 7 (5.9) | 4 (9.3) | 0.453 |
| Positive HBsAg, n (%) | 25 (16.5) | 11 (10.3) | 14 (31.1) | **0.002** |
| Positive HCV antibodies, n (%) | 23 (15.1) | 17 (15.9) | 6 (13.3) | 0.688 |
| HIV infection, n (%) | 16 (10.7) | 12 (11.3) | 4 (9.3) | 0.718 |

† excluding patients with indeterminate test results

tigen (HBsAg) [n=14 (31.1%) vs n=10 (10.3%), p=0.002]. The immunosuppressive conditions of the 18 patients with positive anti-HEV IgG were as follows: liver cirrhosis (n=8), HIV infection (n=4), type 2 diabetes (n=3), lymphoma (n=2), liver transplant (n=2), and one patient had both diabetes and liver cirrhosis. The multivariate logistic regression analysis identified that age, blood transfusion history, immunosuppression conditions and positive HBsAg status were the main factors associated with a positive anti-HEV IgG test result (Table 2).

In terms of geographic distribution, most patients with anti-HEV IgG positive results were from Bucharest (n=22) and the nearest counties such as Arges (n=6), Ilfov (n=4), Teleorman (n=3), Dambovita (n=2), and Prahova (n=2) (Figure 2). The mapping data for seroprevalence of HEV infection in Romania, according to the county of origin, are displayed in Figure 3.

**Table 2. Factors associated with a positive anti-HEV IgG test result by multivariate logistic regression**

| Variable | | OR‡ (95%CI) | aOR§ (95%CI) |
|---|---|---|---|
| Age* | | 1.03 (1.02-1.05) | 1.04 (1.01-1.07) |
| Blood transfusion | No | 1 | 1 |
| | Yes | 2.83 (1.11-7.25) | 2.56 (2.03-14.95) |
| Immunosuppression | No | 1 | 1 |
| | Yes | 2.31 (1.10-4.83) | 1.80 (0.78-4.13) |
| Positive HBsAg | No | 1 | 1 |
| | Yes | 3.94 (1.62-9.57) | 5.51 (2.03-14.95) |

‡OR, odds ratio; §aOR, adjusted odds ratio; *the age OR is for each year increase

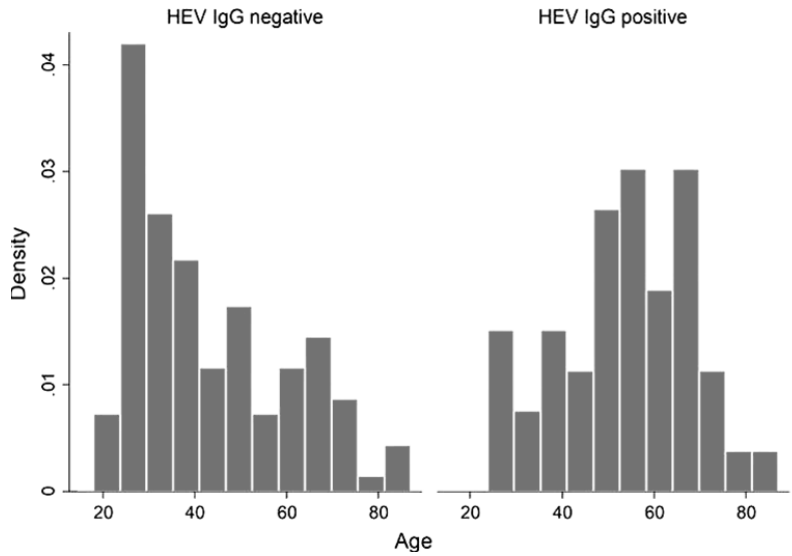


**Fig. 1. Age distribution based on the presence or absence of the serum anti-HEV IgG in the study group**

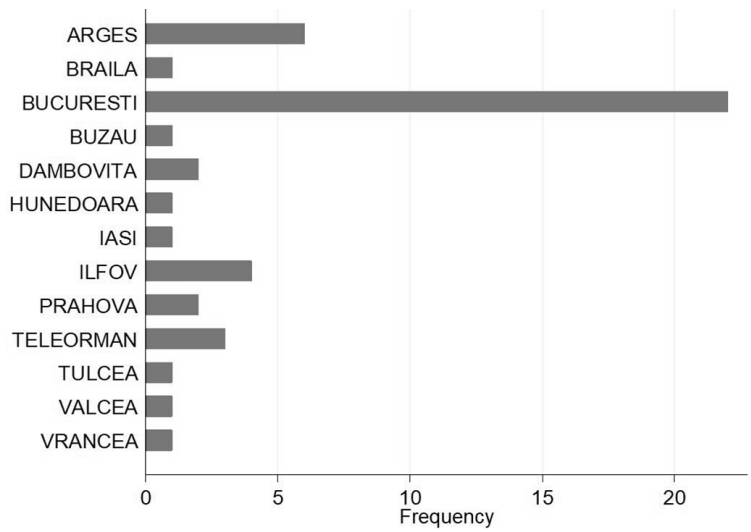


**Fig. 2. Number of patients with positive anti-HEV IgG according to the county of origin**

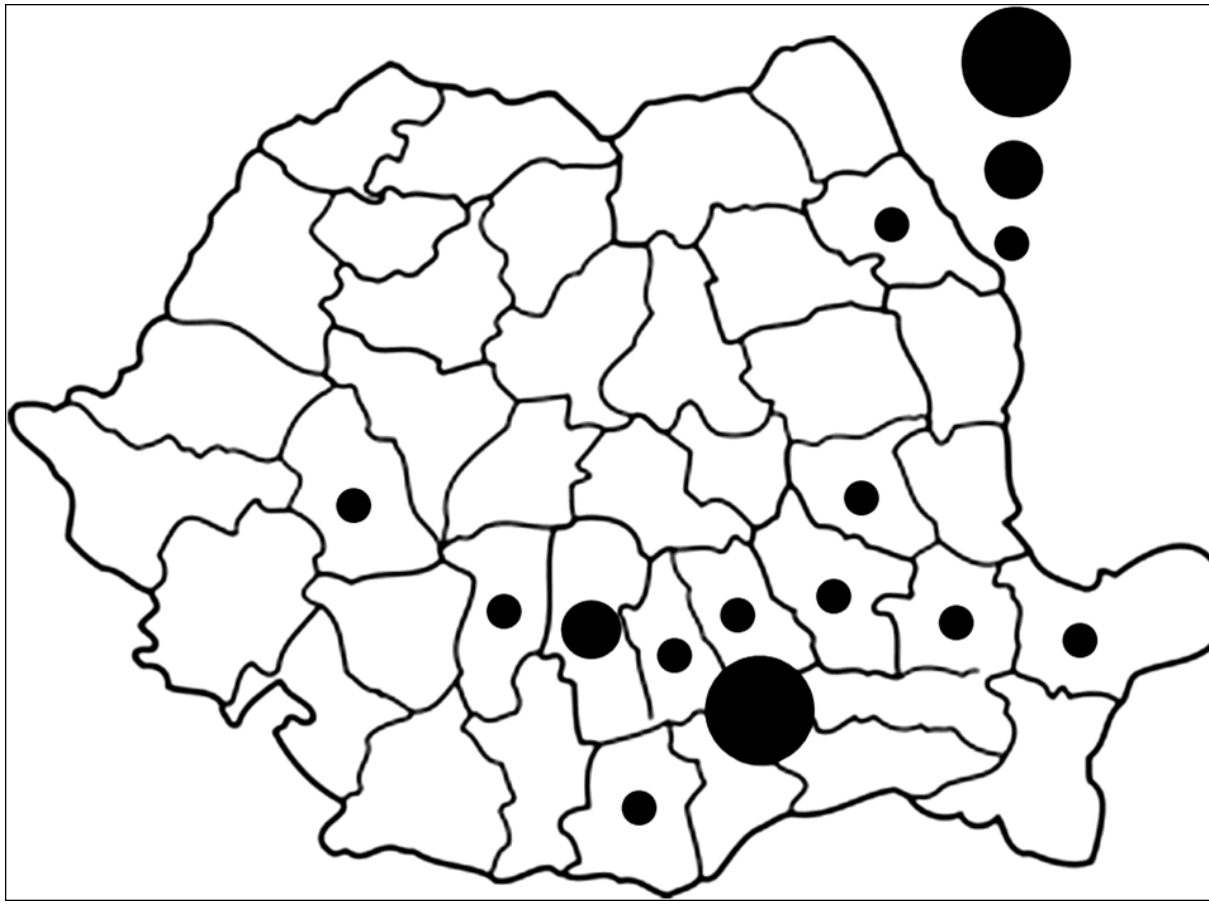

**Fig. 3. Mapping data about seroprevalence of HEV infection in Romania according to county of origin**

## Discussions

We performed this cross-sectional study in order to describe the epidemiology of HEV infection in adult population from a limited geographical area of Romania, focusing on establishing the seroprevalence of anti-HEV IgG and identifying the risk factors associated with HEV infection.

Based on our study, the seroprevalence of anti-HEV IgG was estimated at 26.3% in randomly selected adult patients presenting to the National Institute for Infectious Diseases "Prof Dr Matei Bals" from Bucharest, Romania. Apart from geographical region and study population, one of the major factors that essentially influence the proportion of individuals with positive HEV IgG antibodies is the type of the assay used namely the sensitivity and specificity of the method [8]. Several commercial assays are available for the detection of the serum anti-HEV IgG. Currently, the most commonly used assays are Wantai (WT), Mikrogen (MG), and MP-diagnostics (MP). For the general population the WT method showed significantly higher seroprevalence compared to MG ($p<0.05$) and MP ($p<0.01$) (8). In our study we used the MP diagnostics HEV ELISA kit. Although the population included in the study is not entirely representative of the general population of Romania due to the limited geographic area and the relatively low number

of participants, the HEV seroprevalence found in the present study is higher than that reported by other European countries using the same assessment method (3.9% in Austria, 7.4% in Belgium, 3.3% in Czech Republic, 7.8% in Denmark, 16.3% in France, 4.8% in Germany, 0.9% in Italy, 3.7% in Netherlands, 4.3% in Spain, 4.2% in Switzerland, and 3.2% in United Kingdom) (8). In a recent survey of HEV antibodies in the general population of Portugal the authors reported an overall HEV IgG seroprevalence of 16.3% increasing with age ($p < 0.05$) from 0.6% in the 0-9 years group to 30.1% in people older than 70 years (14). However, the highest prevalence of HEV IgG in Europe has been reported in the southwestern region of France (52.5%) (15,16).

Regarding the risk factors for previous HEV infection, the study found that advanced age was associated with the presence of anti-HEV IgG antibodies. Also, the results of our study were predictable and it was not a surprise to find out that the positivity of anti-HEV IgG was higher in aged patients compared to younger population. The same observation has been reported in all other European countries where the HEV seroprevalence studies have been conducted (14). This finding could be explained by the fact that with the aging of the population there is an increased risk of HEV exposure, especially through contact with source animals within household and farms, hunting activities, agriculture or consumption of improperly cooked meat or meat products.

Other important factors that have been strongly associated with the risk of HEV infection were a history of blood transfusions, immunocompromised status, and the presence of HBsAg. As well as in another studies, no significant difference was found between genders.

Although we did not evaluate the prevalence of HEV IgG in blood donors, our results showed that history of blood transfusions was associated with an increased risk of HEV infection. Despite the fact that this finding might be just a statistical association, we want to highlight that selective screening of blood donors could represent an important strategy to limit HEV infection mainly in immunocompromised recipients who are going to receive blood transfusions. In recent years, a high number of HEV viraemic blood donors have been identified in various large cohorts from different European countries (1 in 616 donors from western Germany, 2015 (17); 1 in 600 donors from the Netherlands, 2014 (18); 1 in 2,481 donors from Scotland, 2016 (19)). Additionally, secondary cases of HEV infection related to blood product transfusion have been reported in countries such as France, Germany, Spain and the United Kingdom (UK) (20). As a result, the risk for and magnitude of transfusion-transmitted HEV infections and the role of HEV RNA screening of blood products are currently a controversial topic in transfusion medicine (21). It has been shown that immunocompromised patients, especially those with solid organ transplantation, who are also more likely to undergo blood transfusions, may develop chronic hepatitis following HEV infection in around 60% of cases and often cirrhosis after a relatively short time interval (22). At this time, several European countries have already implemented different strategies regarding HEV RNA screening of blood donors in order to decrease the risk of transfusion-transmitted HEV infections (21). Thus, a nationwide HEV RNA screening of blood products was introduced in Ireland, the UK, and the Netherlands (21). There are blood transfusion units from countries such as Germany, France, and Switzerland which perform a universal screening for HEV RNA or a selective screening in case of high-risk recipients of blood products (21). Due to the lack of epidemiological data about HEV infection in our population, Romania has not yet taken any action on the HEV RNA screening of blood products.

Although some findings are consistent with the

data published in other studies from Europe, an intriguing observation of our study was related to the possible link between the presence of HBsAg and HEV, which could reflect a common transmission pathway. We need to further investigate this hypothesis by including a large number of hepatitis B infected patients both in acute and chronic phases. This association may be purely coincidental given the lower number of HBsAg positive patients in each group or could reflect potential cross-reactivity between HEV IgG and HBsAg. However, in the literature no data on cross-reactivity between HEV IgG and HBsAg has been published.

The main limitations of our study are related to the limited geographical area from which the patients originated and the relatively low sample size. The selection of the individuals is another limitation because we have not conducted a randomization from the general population but from patients who came to the hospital who are already different from the main population. Therefore, we are not able to comment on risk factors such as hunting considering the small number of patients that declared this activity. However, despite these limitations, there is no doubt that HEV is circulating in our geographical area. As shown in our study, advanced age, immunosuppression status, the history of blood transfusion and the presence of HBsAg were identified as the main risk factors for HEV infection. We believe that our findings will have important epidemiological implications on the public health policy in Romania, representing the starting line for developing a national screening and surveillance program for HEV infection in the general population, including blood donors and in certain patient groups at risk for developing chronic infection, liver cirrhosis or acute-on-chronic liver failure. We also launched the idea of a common route of transmission for HEV and HBV infection, most likely related to sexual exposure.

## Conclusions

In conclusion, we found that autochthonous HEV seropositivity is common in our study population, especially in older patients, those with previous blood transfusions, with immunosuppressive conditions and positive HBsAg. Although the population sample included in the study is not fully representative of the general population of Romania, the prevalence of HEV IgG antibodies was higher than the average reported in other European countries using the same assessment method.

## Author Contributions

Conception and design: VG, OS, ASC, ASC; *Acquisition of data*: VG, IS, AMR; A*nalysis and interpretation of data*: VG, IDO, OS, IS; Literature Search: AMR, IS, IDO; Writing Manuscript: VG, IS, AMR, IDO; Critical Review: VG, IDO, OS, ASC, ASC; *Final approval: VG, IDO, IS, OS, ASC, ASC;*

## Conflict of Interest

There are no conflicts of interest to declare with respect to this article.

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## Abbreviations

aOR, adjusted odds ratio; CI’s, confidence intervals; ELISA, enzyme-linked immunosorbent assay; gt, genotype; HEV, hepatitis E virus; HBV, hepatitis B virus; HBsAg, hepatitis B surface

antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; OR, odds ratio;

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