ORIGINAL RESEARCH

Comparative Analysis on Clinical Characteristics Among Patients with Acute Hepatitis A Virus (HAV) and Patients with Acute Hepatitis E Virus (HEV): A Single-Center Retrospective Study from Bulgaria

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Introduction: The acute viral hepatitis was one of the most common conditions in daily clinical practice varying in different parts of the world. The aim of the present study was to perform a comparative analysis on clinical characteristics among patients with acute hepatitis A virus (HAV) infection and patients with acute hepatitis E virus (HEV) infection admitted to the Military Medical Academy (MMA), Sofia, Bulgaria.

Methods: A retrospective study was performed at MMA, between 1 January 2016 and 31 December 2021. The etiological diagnosis was confirmed by enzyme-linked immunosorbent assay (ELISA) HAV/HEV IgM serology assays.

Results: The current survey included 231 patients with mean age 45.11 ± 16.08 years (95% confidence interval: 43.04–47.19). According to the case definition, inclusion and exclusion criteria, persons were divided into two groups: patients with acute HAV infection (68.4%; 158/231) and patients with acute HEV infection (31.6%; 73/231). Males with HEV had 3.091 times the odds of comorbidity "hypertension" than males with HAV ($p = 0.032$). There were almost equal odds of increased ALT (odds ratio = 0.999; $p = 0.003$) in men with HEV and men with HAV. Females with HEV had 5.161 times the odds of comorbidity "hypertension" compared with females with HAV ($p = 0.049$). We found almost equal odds for elevated ALT in women with HEV and women with HAV (OR = 0.999; $p = 0.025$). In the non-elderly group (<60-year-old), HEV individuals had 4.544 and 10.560 times the odds of comorbidities "hypertension" and "cardiovascular diseases" compared with HAV patients ($p < 0.05$). We found almost equal odds for elevated ALT in HEV patients and HAV participants (OR = 0.998; $p = 0.002$).

Conclusion: The results from the current study may support the physicians daily care for patients with acute HAV and acute HEV.

Keywords: Bulgaria, clinical characteristics, hepatitis A virus, HAV, hepatitis E virus, HEV, single-center study

Introduction

The hepatitis A virus (HAV) was characterized in 1973 by scientific group with team leader Stephen M. Feinstone.[1] HAV has a single-stranded positive-sense RNA genome, and it is part of *Hepatovirus* genus, within the *Picornaviridae* family.[2] According to the World Health Organization (WHO) database in 2016, 7134 individuals died from HAV (this is approximately 0.5% of the mortality due to viral hepatitis).[3] The virus spreads through contaminated water and food, poor sanitary conditions and living environment, worsened personal hygiene and practice of anal/oral sex.[4,5] Most patients with HAV infection have no or few symptoms with mild clinical form mainly in children compared to severe

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clinical forms much more common in adults/elderly.[6–11] Unvaccinated adults are at risk of moderate, severe, or fulminant clinical form of HAV.[12,13] From an-other point of view, in developed countries the incidence of HAV is low.[14] Therefore, in these countries, due to the low circulation of HAV, part of the elderly population may have never encountered HAV or have not been vaccinated and therefore be at increased risk. In this regard, vaccination against HAV is very important because it protects against illness, complications and fatal outcome. HAV does not cause chronic infection in comparison with the other viral hepatitis.[15]

To date in international peer-reviewed journals, there are few articles on HAV infection in Bulgaria. Dimitrova et al reported that the inclusion of the HAV vaccine in the Bulgarian National Vaccination Calendar is recommended for certain risk groups and may help to reduce the circulation of the virus in the Bulgarian population.[16] In 2017, a joint Italian-Bulgarian scientific team presented the first molecular analysis of HAV among 105 patients from Bulgaria.[17] These authors reported that phylogenetic analysis revealed two main sequence groups corresponding to the HAV-IA sub-genotype (74%; 78/105) and HAV-IB sub-genotype (26%; 27/105).[17] In another article, Toseva et al presented data for the overall 52.7% HAV seropositivity among 110 workers in three wastewater treatment plants (WWTPs) in Bulgaria.[18] In 2018, Cella et al analyzed the genetic diversity of HAV-IA and HAV-IB sub-genotypes in Bulgaria.[19] The last published Bulgarian study on HAV recommended the performance of an abdominal ultrasound with high attention to the gallbladder wall in case of acute HAV infection among children.[20] According to the annual epidemiological reports of the European Centre for Disease Prevention and Control (ECDC) in the last years (2011–2021), the frequency of HAV infection in Bulgaria varies widely.[21] For this period Bulgaria's mean notification rate was 28.95 cases per 100,000 population, compared to European Union/European Economic Area (EU/EEA) countries' mean notification rate of 2.52 cases per 100,000 population (Figure 1).[21]

The hepatitis E virus (HEV) was characterized in 1983 by scientific group with team leader Mikhail S. Balayan.[22] These scientists established the fecal-oral route of spread of this new liver disease. HEV is a single-stranded, positive-sense RNA virus in the *Hepeviridae* family.[23] Human HEV belongs to *Paslahepevirus balayani* species, *Paslahepevirus* genus.[23,24] According to the WHO database, every year, 20 million human HEV cases are estimated worldwide, including approximately 3.3 million people with mild, moderate or severe clinical forms of HEV, ie, people with clinical signs and symptoms.[25] Furthermore, WHO estimates that this virus caused 44,000 fatal cases in 2015 (accounting for 3.3% of the mortality due to viral hepatitis).[25] In developing countries HEV genotype (gt) 1 and HEV gt 2 spread via the fecal-oral route (principally via contaminated water and water sources).[26] In developed countries, HEV gt 3 and HEV gt 4 have zoonotic transmission and spread mainly through the consumption of under-cooked animal meat (including pork meat, game meat, pig liver, pork sausages, pates, salami, dry sausages, and others).[27,28] HEV gt 7 (camels and humans) and rat HEV-C1 (rats and humans) are zoonoses.[29–32] To date, HEV gt 5, HEV gt 6 and HEV gt 8 have been only identified in animals.[33,34] Usually HEV infection affects the adults (over 50 years-old).[35,36] In these individuals, the
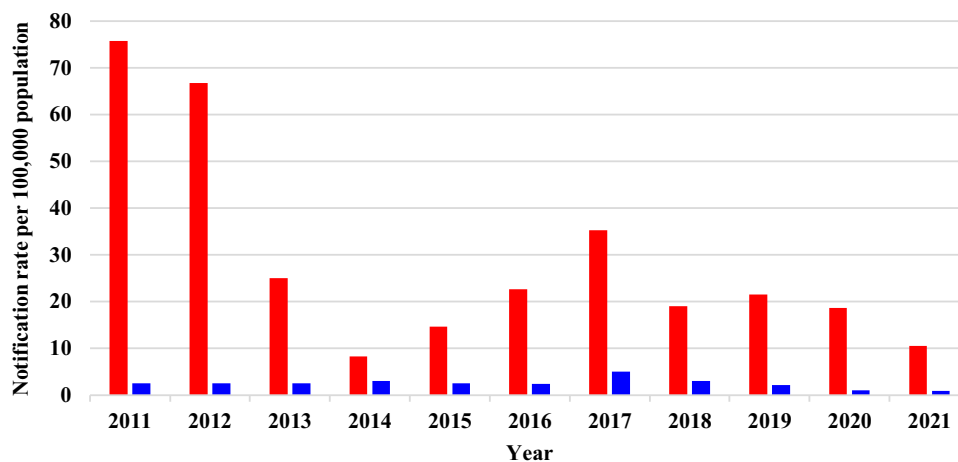
Figure 1 Dynamics of HAV notification rate per 100,000 population in Bulgaria (in red) and EU/EEA (in blue), 2011–2021.

infection can proceed with mild, moderate or severe clinical form. In developing countries, pregnant women are at increased risk (the HEV disease incidence rate was 8-times higher and acute liver failure occurred 13-times more often among pregnant women in comparison to non-pregnant women).[37] In developed countries, immunosuppressed and immunocompromised persons are mainly at increased risk (patients with solid organ transplantation; hematologic malignancy patients; HIV-positive individuals).[38–41] Chronic HEV infection has been established in immunosuppressed and immunocompromised individuals.[38–41] A recombinant hepatitis E vaccine has been developed and applied in China.[42]

In the last years, some important studies on HEV in humans and animals were conducted in Bulgaria and were published in international peer-reviewed journals. In 2014, Teoharov et al reported an overall 9.04% (67/741; 95% CI: 6.9–11.1%) HEV IgG seroprevalence in general population from Plovdiv district, Bulgaria.[43] In 2016, Baymakova et al presented a case series of 20 patients with acute HEV infection from Sofia, Bulgaria.[44] A scientific team of Italian and Bulgarian researchers conducted the first molecular studies of human HEV in Bulgaria.[45,46] In 2021, Baymakova et al reported high HEV seropositivity in Bulgarian blood donors – 25.9% (144/555); general hunters – 48.7% (19/39); and hunters of wild boars – 51.6% (16/31).[47] During the last year, Golkocheva-Markova et al reported 10.9% (34/312) positive HEV antibodies in 312 serum samples on HIV-infected individuals.[48] It is difficult to determine the frequency of acute HEV infection in Bulgaria. On the one hand, ECDC does not prepare HEV annual epidemiological reports. On the other hand, Bulgarian health authorities did not prepare annual epidemiological reports on HEV. National HEV surveillance has been started since 2019. The National Center of Infectious and Parasitic Diseases (NCIPD), Sofia, Bulgaria reported 217 cases of acute HEV in 2019; in 2020–88 cases; in 2021–46 cases; the mean incidence rate was 1.68 per 100,000 population.[49]

The present study aimed to do a comparative analysis on clinical characteristics among patients with acute HAV infection and patients with acute HEV infection from one hospital in Sofia, Bulgaria. To the best of our knowledge, this is the first research that makes a detailed and in-depth comparative analysis (univariate analysis and multivariable analysis) of the clinical characteristics of HAV and HEV infections in both sexes (males and females) and in two important age groups (adults under 60-years-old and adults over 60-years-old).

Materials and Methods
Study Design, Participants and Data Collection

A retrospective survey was conducted between 1 January 2016 and 31 December 2021 at Military Medical Academy (MMA), Sofia, Bulgaria. To date, the MMA includes five multidisciplinary hospitals for active treatment and two hospitals for long-term treatment and rehabilitation. The present study was conducted at the Department of Infectious Diseases in multidisciplinary hospital for active treatment in Sofia, part of MMA. This hospital has over 700 beds, and it is the Bulgarian reference center for liver transplants (more than 70 liver transplants have been performed to date).

Upon admission to the Department of Infectious Diseases, all patients with acute HAV and acute HEV infections were examined by a clinical team including a physician (infectious disease specialist) and nurse. The physician performed the following activities: medical history (personal and family); physical examination; laboratory tests (according to evidence-based medicine for viral hepatitis); and imaging and invasive investigations (according to evidence-based medicine for viral hepatitis). The nurse assisted the physician with the administrative activities of filling out the patient's electronic medical record and settling in the hospital room.

Participants in this study were selected based on medical history, laboratory tests, serological assays, inclusion and exclusion criteria (Figure 2). The necessary information for the survey was extracted from the electronic medical records of patients. For demographics and baseline characteristics, data were collected for sex (male, female); age; length of hospital stay; type of patients (civilians, soldiers); exposure history (travel abroad, contact with ill persons, contact with animals); comorbidities (hypertension, diabetes mellitus, cardiovascular disease, etc.). Clinical signs and symptoms were recorded on the day of admission and included data on dark urine; fatigue; abdominal pain; jaundice; nausea/vomiting; pale stools; and others. The laboratory parameters were extracted from patient records at admission and discharge, and included the following laboratory tests: aspartate aminotransferase (AST); alanine aminotransferase (ALT); gamma-
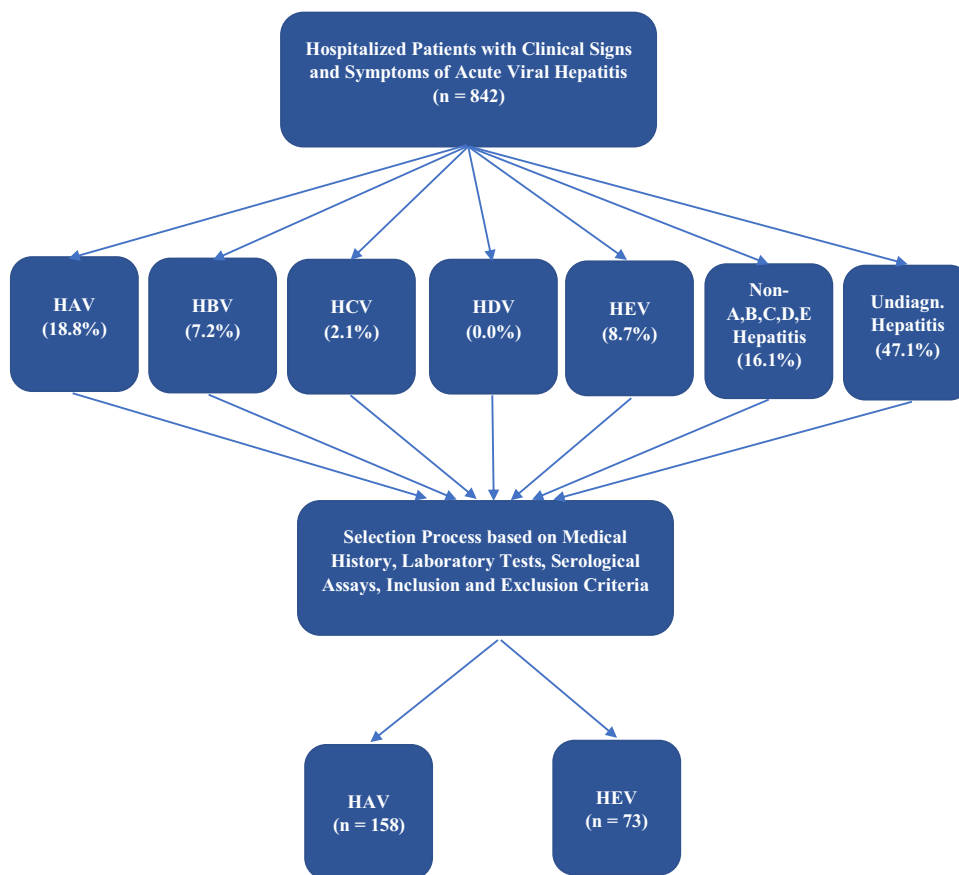
Figure 2 Flow chart showing the selection process of research participants.

glutamyl transferase (GGT); alkaline phosphatase (AP); bilirubin (total, direct); protein (total); albumin; fibrinogen; international normalized ratio (INR); white blood cells (WBC); thrombocytes; and C-reactive protein (CRP).

Case Definition

Acute HAV infection was defined by the presence of clinical signs and symptoms for viral hepatitis, AST/ALT elevation, and positive anti-HAV IgM serology.

Acute HEV infection was defined by the presence of ALT/AST elevation with clinical signs and symptoms for viral hepatitis, and positive results from HEV IgM serology assay.

Inclusion and Exclusion Criteria

The inclusion criteria for the current research: (a) individuals older than 18 years; (b) adults sought primary or secondary medical care in hospital; (c) persons with clinical signs and symptoms for viral hepatitis established by a physician (infectious disease specialist); (d) individuals with elevated liver enzymes; (e) department of virology which has confirmed HAV and/or HEV infections (HAV IgM and/or HEV IgM antibody testing); (f) obtained written informed consent from each patient to participate in a scientific survey.

The exclusion criteria for the present study include: (a) individuals younger than 18 years; (b) persons without clinical signs and symptoms for acute viral hepatitis; (c) individuals with liver enzymes in reference range; (d) negative result for HAV or HEV infection; (e) patients with solid organ transplantation; (f) pregnant women; (g) individuals with persistence of HEV IgM antibodies ≥6 months.

HAV and HEV Serological Tests

Serological diagnosis and analysis were performed in the Department of Virology, MMA, Sofia, Bulgaria, by a highly qualified team led by a clinical virology specialist (physician). From each patient, 5 mL of serum was taken, after that HAV IgM ELISA test and HEV IgM ELISA test according to the instructions of the manufacturer were conducted at the virology department. The collection, transportation and storage of all serum samples were done according to the regulatory requirements of the hospital and the country.

For diagnosis of acute HAV infection, we used the HAVIgM enzyme-linked immunosorbent assay (ELISA) on Dia. Pro (Milan, Italy). The test was used for the determination of IgM class antibodies to HAV in human plasma or sera with the "capture" system. The assay was based on the principle of "IgM capture" where IgM antibodies were first captured by the solid phase coated with anti-IgM antibody. The HAV IgM ELISA test (Dia.Pro, Milan, Italy) has a 100% sensitivity and >98% specificity.

The diagnosis of HEV infection was performed with HEV IgM ELISA test (Dia.Pro, Milan, Italy).[50,51] The test was used for the determination of IgM antibodies to HEV in human plasma or sera. The system "capture" and the principle of "IgM capture" was performed as in the diagnostic process of HAV. The HEV IgM ELISA test (Dia.Pro, Milan, Italy) has a 100% sensitivity and ≥95% specificity.

Ethical Considerations

All patients signed a written informed consent to participate in scientific research upon admission to the hospital. All individuals gave written informed consent for the imaging and invasive procedures conducted on them. Every patient had access to their medical records during the hospital stay and after discharge. The physicians and scientists participating in this research conducted their activities according to the ethical principles of Declaration of Helsinki (adopted in June 1964, last revision in October 2013). The current survey was approved by the Local Ethics Committee of MMA, 1606 Sofia, Bulgaria, who confirmed that the research was in full accordance with all ethical principles and practices.

Statistical Analysis

Statistical analysis was conducted and verified by medical statistics specialist (full professor). Data analysis was performed with the help of SPSS Statistics 21.0 (IBM Corp., Armonk, NY, USA) and Excel 2007 (Microsoft, Redmond, WA, USA). Data were entered and arranged in MS Excel. The distribution of continuous variables was tested using the Kolmogorov–Smirnov test. Normally distributed data were presented as mean ± standard deviation (SD), whereas non-normally distributed data – as median and interquartile range (IQR). Categorical variables were presented in percentage terms. All clinical characteristics obtained from the electronic medical records were compared by Chi-square test, Fisher's exact test, Mann–Whitney test, or *t*-test. Univariate logistic regression was used to assess the risk regarding the type of hepatitis (HAV or HEV) and different indicators. Multivariate logistic regression (enter method) was applied to assess the independent influence of some parameters on the type of hepatitis (HAV or HEV). A p-value <0.05 was considered statistically significant. The final results obtained from the statistical analysis were checked by the other scientists involved in this study.

Results

The current survey included 231 patients with mean age 45.11 ± 16.08 years (95% CI: 43.04–47.19); male – 46.15 ± 16.22 years (95% CI: 43.42–48.88); and female – 43.63 ± 15.83 years (95% CI: 40.44–46.81). The male sex dominated among analyzed individuals (sex ratio: male/female = 1/0.69). According to the case definition, inclusion and exclusion criteria, persons were divided into two groups: patients with acute HAV infection (68.4%; 158/231) and patients with acute HEV infection (31.6%; 73/231). The male sex dominated in persons with HAV (male vs female = 54.4% vs 45.6%) and individuals with HEV (male vs female = 68.5% vs 31.5%) (Table 1). HAV infection had affected younger people compared to HEV infection (HAV vs HEV = 40.7 years vs 54.4 years; p < 0.001). Participants over 50-years-old with HAV were 27.2% (43/158) and those with HEV – 67.2% (49/73). HAV and HEV infections varied during different months of the year (Figure 3). The seasonal distribution of HAV infection compared to HEV infection was as follows:

Table 1 Clinical Characteristics of Bulgarian Patients with Acute Hepatitis A Virus (HAV) Infection and Acute Hepatitis E Virus (HEV) Infection

Characteristics	HAV (n = 158)	HEV (n = 73)	P-value
Sex, n (%)			
Female	72 (45.6)	23 (31.5)	0.043
Male	86 (54.4)	50 (68.5)	
Age, years, mean ± SD	40.7 ± 14.8	54.4 ± 14.5	< 0.001
Age groups, n (%)			
18–29	42 (26.6)	4 (5.5)	< 0.001
30–39	43 (27.2)	6 (8.2)	0.002
40–49	30 (19.0)	14 (19.2)	0.885
50–59	20 (12.7)	21 (28.8)	0.005
≥ 60	23 (14.5)	28 (38.3)	< 0.001
Length of hospital stay, days, mean ± SD	8.5 ± 3.2	7.9 ± 3.9	0.242
Type of patients, n (%)			
Civilians	152 (96.2)	66 (90.4)	0.142
Soldiers	6 (3.8)	7 (9.6)	
Exposure history, n (%)			
Travel abroad	8 (5.1)	4 (5.5)	0.555
Contact with ill persons	6 (3.8)	0 (0.0)	0.180
Contact with animals	0 (0.0)	1 (1.4)	0.316
Comorbidity, n (%)			
Hypertension	18 (11.4)	32 (43.8)	< 0.001
Diabetes mellitus	9 (5.7)	14 (19.2)	0.003
Cardiovascular diseases	8 (5.1)	14 (19.2)	0.002
Malignant diseases	2 (1.3)	7 (9.6)	0.008
Chronic liver diseases	1 (0.6)	6 (8.2)	0.005
COPD	1 (0.6)	3 (4.1)	0.094
Immunodeficiency disorders	0 (0.0)	5 (6.9)	0.003
Clinical signs and symptoms, n (%)			
Dark urine	141 (89.2)	61 (83.6)	0.226
Fatigue	123 (77.8)	68 (93.2)	0.004
Abdominal pain	107 (67.7)	53 (72.6)	0.455
Jaundice	103 (65.2)	48 (65.8)	0.933
Nausea / Vomiting	92 (58.2)	39 (53.4)	0.493
Pale stools	91 (57.6)	35 (47.9)	0.171
Muscle pain	86 (54.4)	37 (50.7)	0.596
Malaise	81 (51.3)	47 (64.4)	0.062
Fever	75 (47.5)	19 (26.0)	0.002
Loss of appetite	49 (31.0)	17 (23.3)	0.227
Joint pain	42 (26.6)	4 (5.5)	< 0.001
Skin rash	1 (0.6)	2 (2.7)	0.235
Laboratory parameters (admission), median (IQR)			
ALT	1529 (613–2516)	460 (167–1254)	< 0.001
AST	621 (251–1601)	266 (98–951)	< 0.001
GGT	266 (147–409)	313 (169–592)	0.292
AP	190 (145–255)	212 (130–346)	0.280
Total bilirubin	94 (61–138)	67 (20–125)	0.012
Direct bilirubin	64 (36–99)	37 (8–85)	0.012

(Continued)

Table 1 (Continued).

Characteristics	HAV (n = 158)	HEV (n = 73)	P-value
Total protein	67 (62–71)	69 (62–74)	0.442
Albumin	35 (32–39)	37 (32–42)	0.040
Fibrinogen	3.7 (2.9–4.1)	3.9 (3.2–4.6)	0.077
INR	1.17 (1.04–1.32)	1.07 (1.01–1.15)	0.011
WBC	5.7 (4.7–7.0)	7.4 (5.6–9.5)	< 0.001
Thrombocytes	225 (180–276)	223 (179–288)	0.864
CRP	8.9 (3.6–18.4)	11.2 (1.7–30.2)	0.526
Laboratory parameters (discharge), median (IQR)			
ALT	341 (225–462)	202 (102–337)	< 0.001
AST	109 (76–158)	79 (41–127)	0.001
GGT	179 (103–252)	240 (137–418)	0.006
AP	186 (137–232)	172 (131–275)	0.773
Total bilirubin	62 (38–86)	41 (20–84)	0.028
Direct bilirubin	26 (16–43)	18 (6–50)	0.067
Total protein	66 (60–70)	63 (57–67)	0.117
Albumin	33 (30–35)	35 (32–38)	0.114
Fibrinogen	3.8 (3.3–4.0)	3.5 (2.8–3.5)	0.311
INR	1.09 (1.03–1.28)	1.13 (1.03–1.19)	0.940
WBC	6.5 (5.5–7.9)	7.1 (5.8–9.6)	0.229
Thrombocytes	327 (227–373)	234 (187–295)	0.018
CRP	4.2 (2.1–10.3)	5.6 (2.2–22.3)	0.280

Notes: Reference range: AST / ALT, 5–40 U/L; GGT, 10–50 U/L; AP, 64–300 U/L; Total bilirubin, 5–21 μmol/L; Direct bilirubin, 0–5 μmol/L; Total protein, 66–87 g/L; Albumin, 40–55 g/L; Fibrinogen, 2.0–4.5 g/L; INR, 0.8–1.1; WBC, 3.5–10.5 × 10⁹/L; Thrombocytes, 140–440 × 10⁹/L; CRP, 0.0–5.0 mg/L.
Abbreviations: SD, standard deviation; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; AP, alkaline phosphatase; INR, international normalized ratio; WBC, white blood cells; CRP, C-reactive protein.

spring – 15.2% vs 31.5% (24/158 vs 23/73); summer – 22.1% vs 17.8% (35/158 vs 13/73); autumn – 39.9% vs 20.6% (63/158 vs 15/73); and winter – 22.8% vs 30.1% (36/158 vs 22/73). In the group of HEV patients, there were more comorbidities than in the group of HAV patients: hypertension (43.8%/11.4%; p < 0.001), diabetes mellitus (19.2%/5.7%;
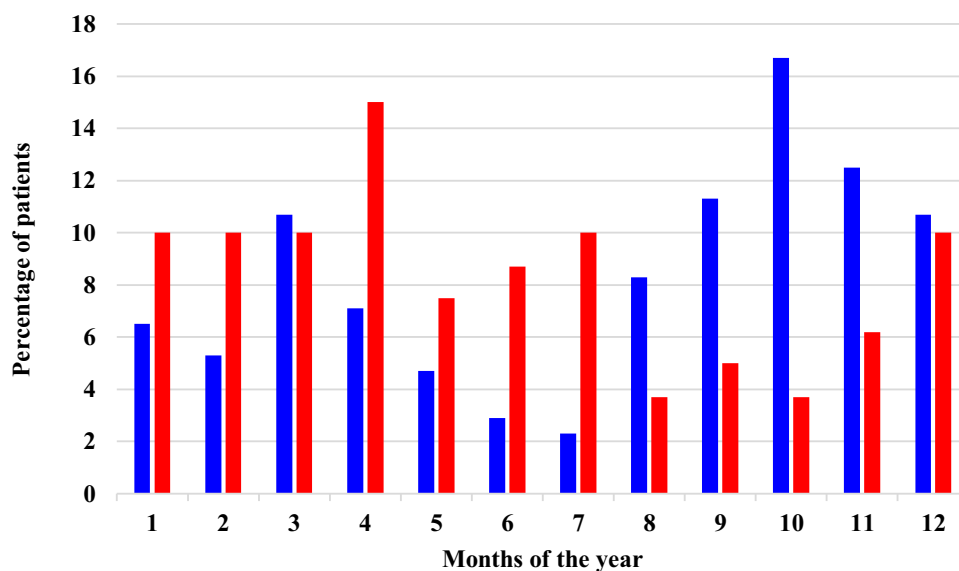
Figure 3 The monthly incidence rates of acute HAV (in blue) and acute HEV (in red).

p = 0.003), cardiovascular diseases (19.2%/5.1%; p = 0.002), and others. The first three most common clinical signs and symptoms in individuals with HAV were dark urine (89.2%), fatigue (77.8%), and abdominal pain (67.7%). The first three most common clinical signs and symptoms in participants with HEV were fatigue (93.2%), dark urine (83.6%), and abdominal pain (72.6%). At admission, AST/ALT was 2.3/3.3 times higher in individuals with HAV compared to patients with HEV (p < 0.001); total bilirubin/direct bilirubin was 1.4/1.7 times higher in HAV vs HEV (p = 0.012). We found the following clinical outcome: discharged with recommendation for outpatient control – HAV/HEV = 157/68 patients; transferred to other hospital unit – HAV/HEV = 1/4; lethal outcome – HAV/HEV = 0/1 (acute liver failure).

In our analysis, participants (n = 231) were divided into two groups by sex: male (n = 136) and female (n = 95) (Table 2). By the conducted univariate logistic regression, we found for the male sex the following: HEV patients had 5.523 times the odds of comorbidity "hypertension" compared with HAV individuals (p < 0.001); HEV participants had 3.761 times the odds of comorbidity "diabetes mellitus" than HAV patients (p = 0.015); and HEV individuals had 4.211 times the odds of comorbidity "cardiovascular diseases" compared with HAV participants (p = 0.007). Furthermore, the clinical sign "fever" was more common in male with HAV than in male with HEV (p = 0.002; OR = 0.274). In addition, upon admission HEV patients had 1.002/1.010 times the odds of elevated AST/ALT than HAV individuals (p ≤ 0.002).

Regarding sex affiliation, a multivariable logistic regression was conducted to assess the relationship between the type of viral hepatitis and some parameters among male and female (Table 3). Males with HEV had 3.091 times the odds of comorbidity "hypertension" than males with HAV (p = 0.032). Furthermore, there was almost equal odds of increased AST (OR = 1.000) and ALT (OR = 0.999) in men with HEV and men with HAV. Females with HEV had 5.161 times the odds of comorbidity "hypertension" compared with females with HAV (p = 0.049).

The second main distribution of the study participants was into two groups, according to their age: non-elderly (<60-year-old; n = 180) and elderly (≥60-year-old; n = 51) (Table 4). By the univariate logistic regression, we found for the non-elderly group the following: HEV participants had 5.687 times the odds of comorbidity "hypertension" than HAV individuals (p < 0.001); HEV patients had 4.094 times the odds of comorbidities "diabetes mellitus" and "cardiovascular diseases" compared with HAV participants (p = 0.042). The clinical sign "malaise" was more common in non-elderly with HEV compared with non-elderly with HAV (p = 0.040; OR = 2.118), while "fever" was more common in HAV individuals than in HEV patients (p = 0.049; OR = 0.493). Upon admission, HEV participants had 1.002 times the odds of elevated AST/ALT compared with HAV individuals (p ≤ 0.001); while elevated total bilirubin and direct bilirubin were more common in HAV patients than in HEV participants (p ≤ 0.005). By the univariate logistic regression, for the elderly group the following was established: HEV individuals had 3.284 times the odds of comorbidity "hypertension" than HAV patients (p = 0.043). The clinical sign "fatigue" was more common in HEV participants compared with HAV individuals (p = 0.016; OR = 14.400), while "pale stools" was more common in HAV patients than in HEV participants (p = 0.042; OR = 0.278).

Regarding age affiliation, a multivariable logistic regression was conducted to assess the relationship between the type of viral hepatitis and some parameters in age groups (Table 5). In the non-elderly group (<60-year-old), HEV individuals had 4.544 times the odds of comorbidity "hypertension" compared with HAV patients (p = 0.011). Also, HEV participants had 10.560 times the odds of comorbidity "cardiovascular diseases" than HAV individuals (p = 0.010). In the elderly group (≥60-year-old), HEV participants had 12.592 times the odds of fatigue compared with HAV individuals (p = 0.029).

Discussion

Acute viral hepatitis is one of the most common infectious illness. Infectious disease units in hospitals provide care for patients with this condition. In this regard, various authors share their experiences with these two infections. HAV infection affects younger individuals compared to HEV infection. Chau et al reported a median HAV age of 27 (12–45) years and median HEV age of 53 (29–73) (p < 0.01).[52] Korean authors presented in their paper a mean HAV age of 28 (22–34) years and mean HEV age of 49 (41–60) years (p < 0.001).[53] Suzuki et al reported a mean HEV age of 57.3 (18–83) years and mean HAV age of 45.2 (22–69) years (p = 0.032).[54] Researchers from Romania presented found that the mean age of HAV participants was 13.3 ± 8.5 years compared with the mean age of HEV persons of 54.3 ± 3.0 years.[55] In several other studies, the reported mean age of HAV patients was lower – 38.0 ± 14.3/29.0 /33.3 ± 7.7 years,[56–58] than

Table 2 Univariate Logistic Regression Showing the Association Between the Type of Viral Hepatitis (HAV and HEV) and Various Parameters Among Male and Female

Parameter	Male (n = 136)						Female (n = 95)					
	Group	n (%) / Median (IQR)	SE	OR	95% CI	P-value	Group	n (%) / Median (IQR)	SE	OR	95% CI	P-value
Comorbidity, n (%)												
Hypertension	HAV	12/86 (13.9)		1.000			HAV	6/72 (8.3)		1.000		
	HEV	23/50 (46.0)	0.421	5.523	2.301–11.992	< 0.001	HEV	9/23 (39.1)	0.604	7.071	2.166–23.084	0.001
Diabetes mellitus	HAV	6/86 (6.9)		1.000			HAV	3/72 (4.1)		1.000		
	HEV	11/50 (22.0)	0.544	3.761	1.295–10.918	0.015	HEV	3/23 (13.0)	0.855	3.450	0.464–18.436	0.148
Cardiovascular diseases	HAV	6/86 (6.9)		1.000			HAV	2/72 (2.7)		1.000		
	HEV	12/50 (24.0)	0.537	4.211	1.469–12.072	0.007	HEV	2/23 (8.6)	1.030	3.333	0.442–25.121	0.243
Clinical signs and symptoms, n (%)												
Dark urine	HAV	80/86 (93.0)		1.000			HAV	61/72 (84.7)		1.000		
	HEV	42/50 (84.0)	0.573	0.696	0.128–1.210	0.394	HEV	19/23 (82.6)	0.640	0.857	0.244–3.004	0.809
Fatigue	HAV	68/86 (79.0)		1.000			HAV	55/72 (76.3)		1.000		
	HEV	46/50 (92.0)	0.585	3.044	0.968–9.577	0.057	HEV	22/23 (95.6)	1.059	6.800	0.852–54.241	0.070
Abdominal pain	HAV	57/86 (66.2)		1.000			HAV	50/72 (69.4)		1.000		
	HEV	37/50 (74.0)	0.395	1.448	0.668–3.140	0.349	HEV	16/23 (69.5)	0.520	1.006	0.363–2.789	0.991
Jaundice	HAV	60/86 (69.7)		1.000			HAV	43/72 (59.7)		1.000		
	HEV	35/50 (70.0)	0.388	1.011	0.473–2.162	0.977	HEV	13/23 (56.5)	0.484	0.877	0.339–2.266	0.786
Nausea / Vomiting	HAV	50/86 (58.1)		1.000			HAV	42/72 (58.3)		1.000		
	HEV	27/50 (54.0)	0.358	0.845	0.419–1.706	0.639	HEV	12/23 (52.1)	0.481	0.779	0.304–2.000	0.604
Pale stools	HAV	53/86 (61.6)		1.000			HAV	38/72 (52.7)		1.000		
	HEV	23/50 (46.0)	0.360	0.530	0.262–1.074	0.078	HEV	12/23 (52.1)	0.480	0.976	0.381–2.498	0.960
Muscle pain	HAV	44/86 (51.1)		1.000			HAV	42/72 (58.3)		1.000		
	HEV	24/50 (48.0)	0.356	0.881	0.439–1.770	0.722	HEV	13/23 (56.5)	0.484	0.929	0.360–2.397	0.878
Malaise	HAV	47/86 (54.6)		1.000			HAV	34/72 (47.2)		1.000		
	HEV	31/50 (62.0)	0.363	1.354	0.665–2.758	0.404	HEV	16/23 (69.5)	0.511	2.555	0.938–6.954	0.066
Fever	HAV	41/86 (47.6)		1.000			HAV	34/72 (47.2)		1.000		
	HEV	10/50 (20.0)	0.414	0.274	0.122–0.618	0.002	HEV	9/23 (39.1)	0.488	0.718	0.276–1.870	0.498
Loss of appetite	HAV	25/86 (29.0)		1.000			HAV	24/72 (33.3)		1.000		
	HEV	13/50 (26.0)	0.400	0.857	0.391–1.879	0.701	HEV	4/23 (17.3)	0.604	0.421	0.129–1.376	0.152
Laboratory parameters (admission), median (IQR)												
ALT	HAV	1890 (731–3100)		1.000			HAV	912 (524–2070)		1.000		
	HEV	464 (153–1088)	0.0002	1.010	1.001–1.020	< 0.001	HEV	268 (185–1403)	0.001	1.001	1.000–1.003	0.033

(Continued)

Table 2 (Continued).

Parameter	Male (n = 136)						Female (n = 95)					
	Group	n (%) / Median (IQR)	SE	OR	95% CI	P-value	Group	n (%) / Median (IQR)	SE	OR	95% CI	P-value
AST	HAV	809 (267–1710)		1.000			HAV	448 (245–1177)		1.000		
	HEV	241 (107–887)	0.0002	1.002	1.001–1.004	0.002	HEV	287 (82–1127)	0.0004	0.999	0.999–1.000	0.145
GGT	HAV	306 (186–504)		1.000			HAV	197 (130–321)		1.000		
	HEV	306 (164–526)	0.0004	1.000	0.999–1.001	0.543	HEV	317 (135–570)	0.001	1.002	1.000–1.005	0.037
Total bilirubin	HAV	107 (78–150)		1.000			HAV	83 (47–122)		1.000		
	HEV	69 (25–146)	0.002	0.999	0.995–1.003	0.614	HEV	28 (13–91)	0.004	0.996	0.989–1.004	0.306
Direct bilirubin	HAV	79 (50–102)		1.000			HAV	54 (27–89)		1.000		
	HEV	38 (10–105)	0.004	0.997	0.990–1.004	0.380	HEV	28 (4–60)	0.006	0.995	0.984–1.006	0.351
CRP	HAV	12.9 (5.2–23.8)		1.000			HAV	6.2 (2.6–15.7)		1.000		
	HEV	10.7 (1.4–30.0)	0.007	1.008	0.994–1.022	0.277	HEV	12.5 (2.2–31.4)	0.010	1.021	1.001–1.042	0.039
Laboratory parameters (discharge), median (IQR)												
ALT	HAV	378 (242–504)		1.000			HAV	300 (198–400)		1.000		
	HEV	218 (115–444)	0.001	0.998	0.997–1.000	0.060	HEV	173 (89–309)	0.002	0.992	0.988–0.997	0.002
AST	HAV	103 (68–136)		1.000			HAV	116 (81–194)		1.000		
	HEV	90 (43–127)	0.002	0.997	0.992–1.001	0.174	HEV	67 (39–98)	0.004	0.992	0.984–1.000	0.040
GGT	HAV	203 (128–274)		1.000			HAV	144 (86–241)		1.000		
	HEV	234 (168–418)	0.001	1.002	1.000–1.003	0.059	HEV	245 (83–396)	0.002	1.004	1.000–1.007	0.031
Total bilirubin	HAV	64 (40–86)		1.000			HAV	60 (35–84)		1.000		
	HEV	49 (25–125)	0.003	0.999	0.993–1.005	0.795	HEV	23 (12–57)	0.009	0.985	0.967–1.003	0.098
Direct bilirubin	HAV	26 (16–42)		1.000			HAV	25 (15–45)		1.000		
	HEV	21 (7–70)	0.005	0.999	0.989–1.008	0.803	HEV	11 (4–38)	0.015	0.983	0.953–1.013	0.253
CRP	HAV	5.4 (2.2–10.5)		1.000			HAV	3.3 (0.9–7.1)		1.000		
	HEV	5.1 (2.3–20.0)	0.016	1.017	0.987–1.108	0.263	HEV	7.9 (1.3–31.7)	0.029	1.046	0.987–1.108	0.128

Abbreviations: SE, standard error; OR, odds ratio; CI, confidence interval.

Table 3 Multivariable Logistic Regression Showing the Relationship Between the Type of Viral Hepatitis and Some Parameters Among Male and Female

Parameter	Group	SE	P-value	OR	95% CI
Male					
Hypertension	HAV			1.000	
	HEV	0.527	0.032	3.091	1.100–8.689
Diabetes mellitus	HAV			1.000	
	HEV	0.679	0.489	1.600	0.423–6.048
Cardiovascular diseases	HAV			1.000	
	HEV	0.648	0.227	2.186	0.614–7.780
Fever	HAV			1.000	
	HEV	0.488	0.148	0.494	0.190–1.284
ALT	HAV			1.000	
	HEV	< 0.001	0.003	0.999	0.998–0.999
AST	HAV			1.000	
	HEV	< 0.001	0.797	1.000	1.000–1.001
Female					
Hypertension	HAV			1.000	
	HEV	0.835	0.049	5.161	1.004–26.529
ALT	HAV			1.000	
	HEV	< 0.001	0.025	0.999	0.998–0.999
GGT	HAV			1.000	
	HEV	0.001	0.128	1.002	0.999–1.005
CRP	HAV			1.000	
	HEV	0.012	0.274	1.014	0.989–1.038

the mean age of HEV individuals – 42.5 (28.0–66.0)/46.0 (20.0–84.0)/57.0 (14.0–86.0) years.[59–61] Regarding our study, the estimated mean ages (HAV patients = 40.7 ± 14.8 years and HEV patients = 54.4 ± 14.5 years; p < 0.001) were similar to the results from studies conducted in Akita, Aomori, Iwate, Miyagi prefectures, Japan,[54] Ogaki city, Japan,[56] and Brno city, Czech Republic.[61]

The review of the scientific literature showed that men may get both infections (HAV and HEV) more often than women. Romanian scientists presented a survey in which male were 100% affected by HEV and 53.9% by HAV.[55] Japanese authors reported in their manuscript that sex distribution male:female was 80:20% for HAV and 78.2:21.8% for HEV.[54] A scientific team from Hong Kong, China, found 25% females with HEV infection vs 75% males with HEV and 34.3% females with HAV infection vs 65.7% males with HAV in their study.[52] Sridhar et al reported that 75% of participants with positive HEV-IgM ELISA were men and only 25% were women.[59] Oh et al found that 69.6% of patients with HEV were males and 67.3% of persons with HAV were men.[53] Regarding the sex distribution among patients with HAV infection in present study, our results (males = 54.4%, 86/158; females = 45.6%, 72/158) were similar to data obtained from a study conducted in Iasi, Romania.[55] As far as HEV gender distribution in the current survey, our data (males = 68.5%, 50/73; females = 31.5%, 23/73) were similar to results established in a study conducted in Zhejiang province, China.[60]

The seasonal and monthly distribution of both infections (HAV and HEV) varies in different regions of the world and in different studies. Our study was conducted among patients living in the temperate climate zone. To date, two studies of clinical characteristics among individuals with HAV and/or HEV living in climatic conditions similar to those of our research have been published by other authors.[54,58] Suzuki et al and Kwon et al carried out their researches in Japan and South Korea, respectively.[54,58] Geographically, these two countries are located on the border between the temperate climate zone and the subtropical climate zone. Therefore, we could potentially and provisionally assume that the studies of Suzuki et al and Kwon et al were conducted in climatic conditions similar to ours. Suzuki et al from Iwate and three neighboring prefectures in Japan reported for an equal distribution of HAV and HEV cases during the warm months

Table 4 Univariate Logistic Regression Showing the Association Between the Type of Viral Hepatitis (HAV and HEV) and Various Parameters Among Age Groups (Non-Elderly and Elderly)

Parameter	Non-Elderly (<60-Year-Old) (n = 180)						Elderly (≥60-Year-Old) (n = 51)					
	Group	n (%) / Median (IQR)	SE	OR	95% CI	P-value	Group	n (%) / Median (IQR)	SE	OR	95% CI	P-value
Comorbidity, n (%)												
Hypertension	HAV	9/135 (6.6)		1.000			HAV	9/23 (39.1)		1.000		
	HEV	13/45 (28.8)	0.477	5.687	2.234–14.477	< 0.001	HEV	19/28 (67.8)	0588	3.284	1.036–10.406	0.043
Diabetes mellitus	HAV	4/135 (2.9)		1.000			HAV	5/23 (21.7)		1.000		
	HEV	5/45 (11.1)	0.695	4.094	1.049–15.976	0.042	HEV	9/28 (32.1)	0.648	1.705	0.479–6.067	0.410
Cardiovascular diseases	HAV	4/135 (2.9)		1.000			HAV	4/23 (17.3)		1.000		
	HEV	5/45 (11.1)	0.695	4.094	1.049–15.976	0.042	HEV	9/28 (32.1)	0.683	2.250	0.590–8.580	0.235
Clinical signs and symptoms, n (%)												
Dark urine	HAV	119/135 (88.1)		1.000			HAV	22/23 (95.6)		1.000		
	HEV	37/45 (82.2)	0.472	0.622	0.246–1.569	0.314	HEV	24/28 (85.7)	1.156	0.273	0.028–2.630	0.261
Fatigue	HAV	108/135 (80.0)		1.000			HAV	15/23 (65.2)		1.000		
	HEV	41/45 (91.1)	0.566	2.562	0.845–7.775	0.097	HEV	27/28 (96.4)	1.108	14.400	1.640–126.443	0.016
Abdominal pain	HAV	92/135 (68.1)		1.000			HAV	15/23 (65.2)		1.000		
	HEV	31/45 (68.8)	0.371	1.035	0.500–2.142	0.936	HEV	22/28 (78.5)	0.635	1.956	0.563–6.795	0.291
Jaundice	HAV	87/135 (64.4)		1.000			HAV	16/23 (69.5)		1.000		
	HEV	26/45 (57.7)	0.351	0.755	0.379–1.503	0.424	HEV	22/28 (78.5)	0.646	1.604	0.452–5.692	0.465
Nausea / Vomiting	HAV	79/135 (58.5)		1.000			HAV	13/23 (56.5)		1.000		
	HEV	24/45 (53.3)	0.346	0.810	0.411–1.597	0.543	HEV	15/28 (53.5)	0.566	0.888	0.293–2.692	0.833
Pale stools	HAV	73/135 (54.0)		1.000			HAV	18/23 (78.2)		1.000		
	HEV	21/45 (46.6)	0.345	0.743	0.378–1.462	0.390	HEV	14/28 (50.0)	0.631	0.278	0.081–0.957	0.042
Muscle pain	HAV	73/135 (54.0)		1.000			HAV	13/23 (56.5)		1.000		
	HEV	25/45 (55.5)	0.346	1.062	0.539–2.092	0.863	HEV	12/28 (42.8)	0.568	0.577	0.189–1.757	0.333
Malaise	HAV	69/135 (51.1)		1.000			HAV	12/23 (52.1)		1.000		
	HEV	31/45 (68.8)	0.365	2.118	1.035–4.333	0.040	HEV	16/28 (57.1)	0.566	1.222	0.403–3.704	0.723
Fever	HAV	68/135 (50.3)		1.000			HAV	7/23 (30.4)		1.000		
	HEV	15/45 (33.3)	0.360	0.493	0.243–0.998	0.049	HEV	4/28 (14.2)	0.705	0.381	0.096–1.517	0.171
Loss of appetite	HAV	42/135 (31.1)		1.000			HAV	7/23 (30.4)		1.000		
	HEV	8/45 (17.7)	0.432	0.479	0.205–1.116	0.088	HEV	9/28 (32.1)	0.608	1.083	0.329–3.562	0.869
Laboratory parameters (admission), median (IQR)												
ALT	HAV	1688 (709–2771)		1.000			HAV	629 (357–1106)		1.000		
	HEV	372 (150–974)	<0.001	1.002	1.001–1.003	< 0.001	HEV	572 (242–1318)	0.001	1.000	0.999–1.001	0.830

Parameter	Group	Value	p	OR	CI	p	Group	Value	p	OR	CI	p
AST	HAV	691 (274–1629)		1.000			HAV	328 (147–599)		1.000		
	HEV	210 (94–846)	0.001	1.002	1.000–1.004	0.001	HEV	317 (149–1105)	0.001	1.000	0.999–1.001	0.565
GGT	HAV	268 (156–409)		1.000			HAV	195 (134–400)		1.000		
	HEV	244 (111–490)	0.001	1.001	1.000–1.002	0.142	HEV	334 (289–679)	0.001	1.001	0.999–1.002	0.345
Total bilirubin	HAV	92 (64–125)		1.000			HAV	156 (34–203)		1.000		
	HEV	49 (14–98)	0.004	0.989	0.982–0.997	0.005	HEV	121 (37–248)	0.003	0.002	0.996–1.007	0.559
Direct bilirubin	HAV	62 (36–89)		1.000			HAV	104 (36–130)		1.000		
	HEV	26 (3–60)	0.006	0.984	0.973–0.994	0.003	HEV	81 (35–141)	0.004	1.002	0.993–1.011	0.683
CRP	HAV	7.9 (3.1–17.1)		1.000			HAV	13.3 (7.8–21.2)		1.000		
	HEV	7.9 (1.4–28.2)	0.008	1.008	0.991–1.024	0.354	HEV	19.5 (7.1–31.8)	0.010	1.013	0.993–1.033	0.208
Laboratory parameters (discharge), median (IQR)												
ALT	HAV	348 (238–476)		1.000			HAV	273 (167–397)		1.000		
	HEV	199 (90–324)	0.001	0.997	0.995–0.999	0.008	HEV	266 (175–395)	0.002	1.000	0.996–1.004	0.952
AST	HAV	108 (76–155)		1.000			HAV	136 (76–165)		1.000		
	HEV	71 (36–123)	0.003	0.993	0.987–0.999	0.024	HEV	85 (56–131)	0.004	0.996	0.989–1.003	0.244
GGT	HAV	173 (99–240)		1.000			HAV	229 (139–331)		1.000		
	HEV	212 (90–393)	0.001	1.002	1.000–1.004	0.067	HEV	287 (219–512)	0.001	1.001	0.999–1.003	0.332
Total bilirubin	HAV	60 (36–82)		1.000			HAV	71 (52–113)		1.000		
	HEV	31 (14–56)	0.006	0.987	0.975–0.999	0.041	HEV	68 (29–145)	0.006	1.003	0.991–1.014	0.648
Direct bilirubin	HAV	24 (15–41)		1.000			HAV	32 (23–57)		1.000		
	HEV	11 (3–25)	0.011	0.979	0.958–1.000	0.054	HEV	44 (14–81)	0.011	1.009	0.988–1.030	0.396
CRP	HAV	3.4 (1.6–7.7)		1.000			HAV	11.3 (7.4–22.6)		1.000		
	HEV	2.7 (1.0–20.0)	0.024	1.040	0.993–1.090	0.096	HEV	14.3 (3.4–24.2)	0.017	1.003	0.971–1.037	0.853

Table 5 Multivariable Logistic Regression Showing the Relationship Between the Type of Viral Hepatitis and Some Parameters Among Age Groups (Non-Elderly and Elderly)

Parameter	Group	SE	P-value	OR	95% CI
Non-elderly (<60-year-old)					
Hypertension	HAV			1.000	
	HEV	0.593	0.011	4.544	1.420–14.534
Diabetes mellitus	HAV			1.000	
	HEV	0.866	0.690	1.413	0.259–7.710
Cardiovascular diseases	HAV			1.000	
	HEV	0.920	0.010	10.560	1.740–64.079
Malaise	HAV			1.000	
	HEV	0.437	0.319	1.545	0.656–3.639
Fever	HAV			1.000	
	HEV	0.442	0.147	0.527	0.221–1.254
ALT	HAV			1.000	
	HEV	< 0.001	0.002	0.998	0.997–0.999
GGT	HAV			1.000	
	HEV	0.001	0.276	1.001	1.000–1.002
Elderly (≥60-year-old)					
Hypertension	HAV			1.000	
	HEV	0.661	0.069	3.323	0.911–12.128
Fatigue	HAV			1.000	
	HEV	1.162	0.029	12.592	1.291–122.848
Pale stools	HAV			1.000	
	HEV	0.687	0.178	0.396	0.103–1.523

(April–September) and cold months (October–March) of a year.[54] Kwon et al noted the peak of HAV cases in the period of April to August in their nationwide multicenter survey of 4218 participants.[58] The results of our survey showed that the majority of HAV and HEV cases are observed in the cold months (October–March) of the year. The reasons for the varieties between our results and those reported by other authors may be different. First, the respective study designs varied. Second, different hygiene and eating habits exist in different parts of the world. Third, the serological assay may influence the data obtained. Fourth, the vaccination policy against HAV differs in different countries around the world. Fifth, different tourist preferences and period of visit to high-risk or low-risk areas for contracting HAV or HEV infection. Due to the diversity of all these reasons, it is very hard to determine the risk factors for seasonal and monthly distribution of HAV and HEV infections.

The different scientists reported different leading clinical signs and symptoms among patients with acute HAV or acute HEV. A Romanian study on clinical characteristics of HAV and HEV presented different clinical symptoms.[55] Mihai et al noted that HAV participants had clinical symptoms only (n = 269).[55] HEV participants were only three and therefore no clinical signs were announced.[55] Consequently, we could hardly make an adequate comparison of our results and those from Romanian study. Mihalcin et al from The Czech Republic reported the main clinical symptoms in 173 patients with acute HEV infection: jaundice, myalgia, arthralgia, low-grade fever, and abdominal pain.[61] Our results were similar to those found in the scientific literature. We found that statistically significant clinical signs and symptoms in our patients with acute HAV and acute HEV were fatigue (p = 0.004), fever (p = 0.002), and joint pain (p < 0.001).

Researchers from different parts of the world reported elevation of some laboratory characteristics in acute HAV and acute HEV infections. Chau et al found that few laboratory parameters were statistically significant in HAV patients compared with HEV patients: bilirubin – 79 (6–469) µmol/L vs 153 (33–680) µmol/L, p < 0.01; prothrombin time – 10 (10–18) sec vs 13 (10–26) sec, p < 0.01; prolonged prothrombin time – 8 (8)% vs 7 (30)%, p = 0.01; and hypoalbuminemia – 3 (3)% vs 4 (17)%, p = 0.02.[52] Scientists from Gyeongsang province, South Korea presented that important laboratory factors for acute HAV and acute HEV infection were AST – 1337 (674–2578) U/L vs 292 (103–852) U/L, p <

0.001, and ALT – 2357 (1156–2603) U/L vs 525 (109–1062) U/L, p < 0.001.[53] Suzuki et al reported high levels of liver indicators among individuals with acute HAV (AST – 2459 U/L; ALT – 3081 U/L; total bilirubin – 44 µmol/L) and those with acute HEV (AST – 1267 U/L; ALT – 1483 U/L; total bilirubin – 38 µmol/L).[54] Authors from Zhejiang province, China conducted a retrospective survey among 78 patients with acute HEV infection.[60] These scientists divided the participants into two groups: ≥60-year-old (elderly) and <60-year-old (non-elderly).[60] The authors found the following statistically significant results when comparing the laboratory parameters between the two groups (elderly vs non-elderly) : ALT – 1084 ± 1100 U/L vs 2493 ± 1664 U/L (p = 0.008); total bilirubin – 256 ± 162 µmol/L vs 73 ± 70 µmol/L (p < 0.001); and direct bilirubin – 170 ± 117 µmol/L vs 41 ± 38 µmol/L (p = 0.001).[60]

Our results were similar to the results of some authors, but also differed from other studies on this topic. The analysis of the literature on the subject (HAV and HEV infections) found both common characteristics and differences. For example, all surveys established that males were more commonly affected than females. In addition, the mean age of individuals with acute HAV was lower than the mean age of persons with acute HEV (most often the difference ranged from 10–15–20 years).[52–55] Consequently, people in childhood or young age more frequently encountered HAV. Then clinical symptoms were noted, and mild, moderate or severe clinical forms of the illness were developed. Also, the improvement of hygiene and living conditions were a potential way, which leading to an increase in age getting HAV. But the older age was a risk factor for a severe clinical form of acute HAV infection. Furthermore, a serious risk factor for the spread of HAV infection is contaminated food. For example, Tominaga et al reported on HAV outbreak associated with a revolving sushi bar occurred in Chiba, Japan.[62] In this regard, contaminated food, poor sanitary conditions and worsened personal hygiene can be important risk factors for the spread of HAV infection. An advantage of HAV infection is that the severe complications and liver failure are rare compared to other viral liver infections.

HEV infections are more frequently presented with clinical signs and symptoms in individuals over 50 years of age.[35,63,64] The consumption of under-cooked animal meat (incl. pork meat, pig liver, etc.) was the route of HEV transmission, therefore we could reasonably conclude that all age groups were at risk of HEV infection. However, individuals younger than 50 years of age were unlikely to present a clinical form of HEV compared with individuals over 50 years of age. One of the potential reasons for this could be that the elderly had more common comorbidities (hypertension, diabetes mellitus, etc.) and this was a prerequisite for a more severe course of the infection. Another potential reason was the better immune system response in younger individuals compared with older individuals. So, it could be a possible reason for asymptomatic or mild clinical form of HEV in young individuals. These are scientific hypotheses that could be confirmed or rejected in future research on this topic.

The current survey has some limitations that need to be addressed. First, this is a retrospective study; therefore, data were obtained from electronic medical records, ie, additional clarifying information cannot be implemented. Second, we present a single-center experience. In this regard, it would be better to realize a multicenter study, which would reduce the possibility of omissions and errors. Third, the research involved a small number of participants. This limitation cannot be avoided because the topic of the study is acute HAV and acute HEV, ie, the participants were individuals with a clinical form (disease) of these two infections. Despite these limitations, this research has its merits. This is the first survey that makes a detailed and in-depth comparative analysis (univariate analysis and multivariable analysis) of the clinical characteristics of HAV and HEV infections in both sexes (males and females) and in two important age groups (non-elderly and elderly). To date, all studies on the topic have only made a general comparison between the two infections (HAV and HEV).[52–55] Therefore, our results add to the knowledge of the clinical characteristics in patients with acute HAV and acute HEV.

Conclusion

Acute viral hepatitis may cause a severe clinical form of illness, serious complications and a fatal outcome. In this regard, the analysis of clinical characteristics among patients with acute HAV and acute HEV has important implications for daily clinical practice. It could optimize medical care for these patients. By our results, the comorbidity "hypertension" and ALT were important when comparing males and females with HAV and HEV infections. We found statistically significant results for comorbidities (hypertension and cardiovascular disease) and ALT in non-elderly patients (<60-year-old) comparing HAV and HEV. In the elderly group (≥60-year-old), fatigue was a significant parameter for patients with

HAV infection compared with HEV infection. Furthermore, another important conclusion – HEV was associated more frequently with comorbidities. So, the results from the current study may support the physicians daily care for patients with acute HAV and acute HEV. Although these infections rarely lead to a severe clinical form, they continue to have an important place in infectious disease specialists' work. Therefore, improving knowledge about acute viral hepatitis is a good prerequisite for improving medical care for these patients.

Ethical Approval

This study was conducted in accordance with the Military Medical Academy, Sofia, Bulgaria research ethical guidelines and according to ethical principles included in the Declaration of Helsinki (adopted in June 1964, last revision in October 2013). Ethical approval for this survey was obtained from the Local Ethics Committee of Military Medical Academy, 1606 Sofia, Bulgaria (MMA, 02/2022).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest.

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