Original article

# VIRAL HEPATITIS E IN PLEVEN REGION – CLINICAL, LABORATORY AND EPIDEMIOLOGICAL CHARACTERISTICS

Galya Gancheva
*Department of Infectious Diseases, Epidemiology, Parasitology and Tropical Medicine, Faculty of Public Health, Medical University-Pleven, Bulgaria .*

**ABSTRACT:**

Viral hepatitis E (VHE) is endemic in most countries nowadays. Our **purpose** was to analyze the characteristics of VHE in the Pleven region.

**Material and Methods:** We performed a retrospective analysis of clinical, laboratory, and epidemiological data of 33 consecutive serologically confirmed cases of VHE treated in Clinic of Infectious Diseases at University Hospital – Pleven (2016-2019) (18 male – 56%, mean age 59±15 years). Statistical methods – t-test and $\chi^2$ test (for parametric and non-parametric distributions, respectively; $P<0.05$ was considered to be significant).

**Results:** Totally 283 cases of hepatitis were treated in the Clinic (2016-2019) (cases of VHE- 12%). Fifty-five percent of VHE cases were older than sixty years (79% – urban residents); 39% acquired the disease during March-April. Only in two cases had contacts with pigs. The commonest symptoms were hepatomegaly (100%), fatigue (94%), darkness of urine (92%), jaundice (79%), anorexia (76%), splenomegaly (67%), nausea and vomiting (58%). The jaundice was protracted (median six days). Laboratory investigations- mild leukocytosis (21%), thrombocytopenia (18%), increased serum bilirubin with a prevalence of direct fraction (82%; mean ± sd 94±91 µmol/L; 95% CI 63÷125), increased aminotransferases in 100% (ASAT mean ± sd 812±629 IU/L; 95% CI 598÷1027; ALAT mean ± sd 1327± 790 IU/L; 95% CI 1058÷1597), mild to moderately increased alkaline phosphatase and GGT (90% and 100%, respectively). All of the patients were successfully treated with glucose infusions, hepatoprotective drugs and vitamins (mean 10 days).

**Conclusions:** The clinicians should consider VHE in the diagnostic process. The disease affects mainly older ages, and jaundice is protracted.

**Keywords:** viral hepatitis E, serum bilirubin, aminotransferases, treatment,

## INTRODUCTION

Infection with hepatitis E virus (HEV) is a global health problem. It is a significant cause of morbidity and mortality [1]. The knowledge about viral hepatitis E (VHE) rose, and our understanding of the disease had changed completely over the past decade. Previously, VHE had been observed only in certain developing countries. Nowadays, we know that HEV is endemic in most high-income countries. Moreover, it is largely a zoonotic infection [2, 3]. The locally acquired (autochthonous) VHE is the commonest cause of acute viral hepatitis in many European countries. Despite the increased knowledge, there are unclear aspects. Therefore, clinicians continue to make conclusions based on the evolving evidence [1].

Discovery of hepatitis E had begun in 1978 when an epidemic of hepatitis in Kashmir was investigated [4, 5]. The etiology of VHE was discovered in 1983 by Balayan MS. Then Soviet troops in Afghanistan were affected by large outbreaks of hepatitis negative for hepatitis A virus (HAV) and hepatitis B virus (HBV). The scientists ingested a pooled sample of affected soldiers' stool. Later he developed hepatitis, and in his stool was found a new virus by electron microscopy [6]. The genome of this new virus was cloned and named HEV [7]. The sequencing of HEV RNA allowed the development of enzyme-linked immunoassays (ELISA) for anti-HEV antibody. Since several studies had shown that anti-HEV antibody were common in the United States and other developed countries. Also, high rates of antibody positivity had found in several mammals, particularly swine [7, 8]. A swine strain of HEV was identified and classified as genotype 3 in 1997. Cases of acute hepatitis due to genotype 3 HEV were reported in humans in the United States [9] and later in Europe [2, 10-12], New Zealand, and Australia [quoted in 9]. Another swine strain (genotype 4) was identified in Japan [13]. In the past several years, sporadic locally acquired cases of genotype 3 and 4 HEV infection had been increasingly reported in developed countries. Cases of acute liver failure, chronic hepatitis, cirrhosis, and extra-hepatic disorders due to hepatitis E also had been observed [14-16]. Nowadays, hepatitis E infection is found worldwide. Two different epidemiological patterns are observed. According to the first, hepatitis E is found in resource-poor areas with frequent water contamination. The second is in areas with safe drinking water supplies [10].

Thorough investigations upon VHE had realized over the past two decades [17]. The first human case in Bulgaria had been reported by Teoharov et al. in 1995

[18], and since 2008 the disease had been investigated in the country [19, 20]. Several authors presented data for HEV infection among Bulgarian patients [21-26]. However, there are still unclear aspects about this infection in our country.

The **aim** of our study was to analyze the peculiarities in characteristics of VHE in the Pleven region during the last years.

## MATERIALS AND METHODS:
### Study Design
We performed a retrospective analysis of clinical, laboratory and epidemiological data of 33 consecutive serologically confirmed cases of VHE treated in the Clinic of Infectious Diseases at University Hospital – Pleven (2016-2019). Totally 283 cases of viral hepatitis were serologically tested by ELISA assays for anti-HEV IgM, anti-HAV IgM, HBs Ag, anti-HBc IgM, and anti-HCV. Thirty-three of these were with positive tests for anti-HEV IgM, and they were included in the present study.

After a review of the literature, we performed a comparative analysis of demographic, epidemiological, clinical characteristics and laboratory parameters in four foreign and two Bulgarian series of VHE. A literature search was done analyzing the literature in PubMed databases and Bulgarian medical databases (English and Bulgarian languages sources). We used keywords "Hepatitis E virus" and "Bulgaria" and "HEV" and "Hepatitis E virus infection" and "HEV infection". The comparative analysis included original articles and brief reports. Articles with missing data for the number of investigated individuals; case reports, and letters to the editor had been excluded. The sources published within the past 25 years (January 1995 – September 2019) were preferable.

### Ethics Statement
The study was performed according to the principles of the Declaration of Helsinki. Participation in the study was after written informed consent from each person before the medical examination.

### Statistical Analysis
Statistical methods – t-test and $\chi^2$ test had been used (for parametric and non-parametric distributions, respectively). The results obtained from the majority of studies do not allow detailed statistical analysis. Therefore, basic statistical indicators such as confidence interval (CI), standard deviation (SD), etc., were applied. Statistical analysis was performed by Excel 2007 (Microsoft, Redmond, Washington, USA) and SPSS Statistics 19.0 (IBM Corp., Armonk, New York, USA). A $P$-value < 0.05 was considered statistically significant.

## RESULTS:
Totally 283 cases of acute viral hepatitis were treated in the Clinic (2016-2019). Cases of VHE were 12% (fig. 1).

**Fig. 1.** Etiological structure of the cases with different types of viral hepatitis
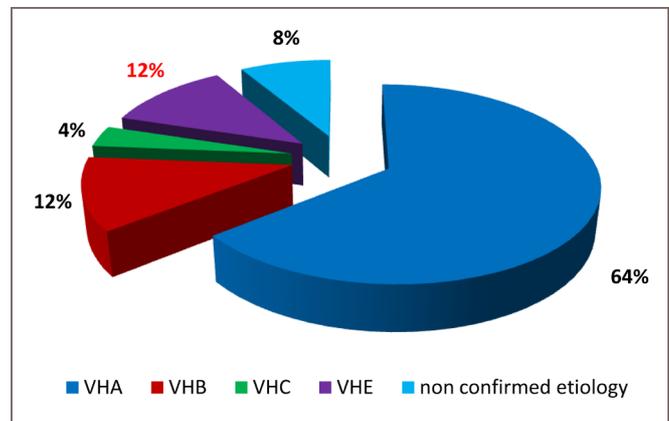


Demographic characteristics of the patients were as follows: the mean age was 59 years (median 62 years; from 16 to 77 years old), and 55% were older than sixty years. Eighteen of the patients were male (55%), and twenty-six (79%) – urban residents.

Epidemiological analysis revealed that 39% of cases had acquired the disease during March and April (18% and 21%, respectively). Only in two of cases had contacts with pigs. Two of the patients had travelled abroad within one month before the disease, and eight of them (24%) had blood manipulations (half of them within few months before admission).

Co-morbidity had been presented in twenty-six cases (79%), and ten of them had more than one concomitant disease. Hypertonic disease and diabetes mellitus had been registered most frequently (in fifteen and five patients, respectively).

The commonest symptoms were hepatomegaly (100%), fatigue (94%), the darkness of urine (91%), jaundice (79%), anorexia (76%), splenomegaly (67%), and nausea (58%). Fever, chills, sweating, fatigue, nausea and vomiting are significantly reduced after admission, but the appetite worsens ($P$ <0.05). The prevalence of clinical signs and symptoms and their dynamics before admission and during the hospital period have been shown in fig. 2 and fig. 3.

**Fig. 2.** Prevalence of clinical signs and symptoms before admission and during the hospital period
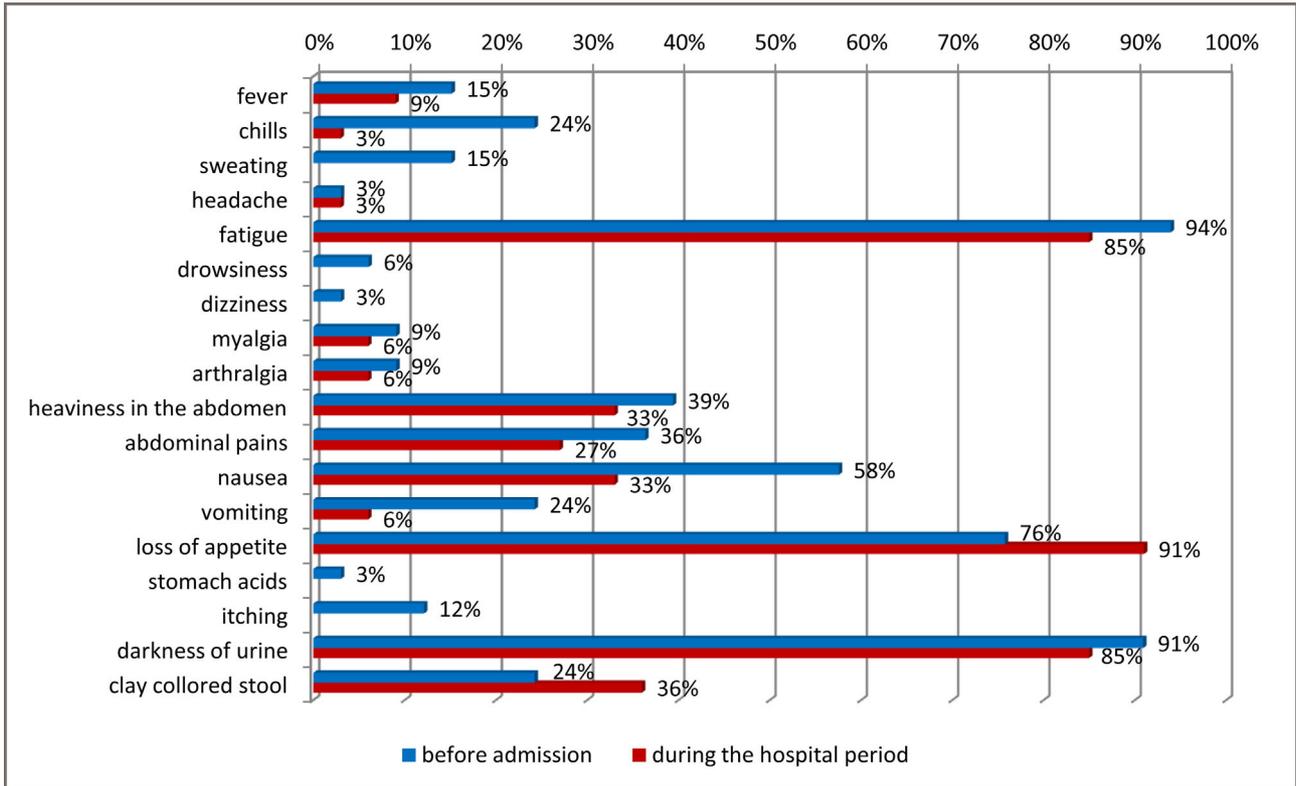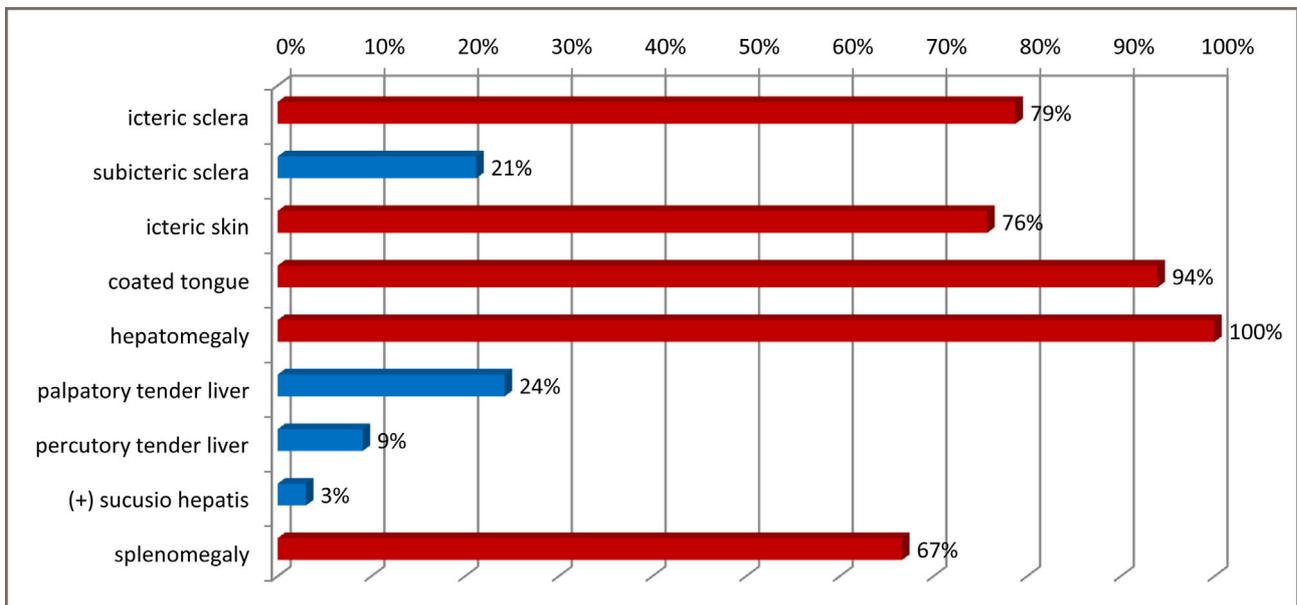


Fig. 2 bar chart: before admission (blue) and during the hospital period (red)

| Symptom | before admission | during the hospital period |
|---|---|---|
| fever | 15% | 9% |
| chills | 24% | 3% |
| sweating | 15% | |
| headache | 3% | 3% |
| fatigue | 94% | 85% |
| drowsiness | 6% | |
| dizziness | 3% | |
| myalgia | 9% | 6% |
| arthralgia | 9% | 6% |
| heaviness in the abdomen | 39% | 33% |
| abdominal pains | 36% | 27% |
| nausea | 58% | 33% |
| vomiting | 24% | 6% |
| loss of appetite | 76% | 91% |
| stomach acids | 3% | |
| itching | 12% | |
| darkness of urine | 91% | 85% |
| clay collored stool | 24% | 36% |

**Fig. 3.** Prevalence of clinical signs and symptoms during the hospital period



Fig. 3 bar chart

| Sign | value |
|---|---|
| icteric sclera | 79% |
| subicteric sclera | 21% |
| icteric skin | 76% |
| coated tongue | 94% |
| hepatomegaly | 100% |
| palpatory tender liver | 24% |
| percutory tender liver | 9% |
| (+) sucusio hepatis | 3% |
| splenomegaly | 67% |

Laboratory investigations revealed mild leukocytosis (21%), thrombocytopenia (18%), increased serum bilirubin with a prevalence of direct fraction (82%; mean ± sd 94±91 μmol/L; 95% CI – 63÷125), increased aminotransferases in 100% (ASAT mean ± sd 812±629 IU/L; 95% CI – 598÷1027; ALAT mean ± sd 1327± 790 IU/L; 95% CI – 1058÷1597), mild to moderately increased alkaline phos-phatase and GGT (90% and 100%, respectively). The serum levels of bilirubin, ASAT and ALAT had increased after admission (P <0.0005) in the absence of cholestasis – the levels of GGT and alkaline phosphatase had gradually decreased. It is probably that hypoalbuminemia supports the worsening of bilirubin metabolism. The dynamics of laboratory parameters during the hospital treatment of the patients have been shown in table 1.

**Table 1.** Laboratory investigations

| Parameters | Reference range | ≠N % | On admission mean ± SD (min-max) | 95% CI | During the hospital period mean ± SD (min-max) | On discharge | P |
|---|---|---|---|---|---|---|---|
| Hemoglobin (g/L) | 120-188 | 12 | 131 ± 17 (90 - 165) | 125 - 137 | 124 ± 11 (106 - 143) | 121 ± 19 (100 - 161) | >0.05 |
| WBC (cells x $10^9$ /L) | 4.0-11.0 | 21 | 8.4 ± 4.2 (4.4 – 25.3) | 6.7 - 9.9 | 7.5 ± 3.7 (4.2 - 16.9) | 7.7 ± 2.7 (3.7 -11.6) | >0.05 |
| Granulocytes (%) | 50-80 | 17 | 61 ± 10 (38 - 85) | 58 - 65 | 62 ± 17 (32 - 85) | 63 ± 19 (33 - 86) | >0.05 |
| Lymphocytes (%) | | 13 | 30 ± 10 (7 - 57) | 25 - 35 | 27 ± 14 (10 - 49) | 30 ± 16 (8 - 53) | >0.05 |
| Platelets (cells x $10^9$ /L) | 150-400 | 18 | 229 ± 85 (52 - 419) | 200 - 258 | 224 ± 86 (107 - 354) | 272 ± 77 (132 - 399) | >0.05 |
| Total bilirubin (µmol/L) | 3.4.2021 | **82** | 94 ± 91 (6.7 - 378) | 63 - 125 | 120 ± 107 (22.4 - 334) | 42 ± 32 (4.7 - 116) | **<0.0025** |
| Direct bilirubin (µmol/L) | 0.8-8.5 | **96** | 78 ± 68 (3.8 - 374) | 45 - 111 | 106 ± 96 (19 - 281) | 34 ± 30 (1.9 - 103) | **<0.01** |
| ASAT (IU/L) | ≤37 | **100** | 812 ± 629 (67 - 3003) | 598 - 1027 | 838 ± 772 (56 - 3370) | 72 ± 49 (27 - 268) | **<0.0005** |
| ALAT (IU/L) | ≤40 | **100** | 1327 ± 790 (80 - 3516) | 1058 - 1597 | 1441 ± 753 (134 - 3427) | 216 ± 104 (38 - 480) | **<0.0005** |
| GGT (IU/L) | 15-28 | **100** | 358 ± 221 (59 - 922) | 282 - 433 | 297 ± 235 (58 - 1035) | 273 ± 192 (46 - 606) | >0.05 |
| Alkaline phosphatase (IU/L) | 50-260 | 90 | 269 ± 165 (76 - 782) | 209 - 329 | 232 ± 73 (117 - 319) | 184 ± 48 (74 - 233) | **<0.01** |
| Total protein (g/L) | 58-80 | 4 | 69.6 ± 5.2 (59 - 77) | 67.5 - 71.6 | 61.6 ± 9.9 (53 - 75) | 58.2 ± 7.2 (52 - 65) | **<0.005** |
| Albumins (g/L) | 35-55 | 12 | 40.6 ± 5.0 (31 - 49.1) | 38.6 - 42.5 | 35.3 ± 2.2 (33 - 38) | 33.9 ± 2.9 (30.6 - 36) | **<0.0005** |
| Fibrinogen (g/L) | 2.0-4.5 | 3 | 3.2 ± 0.8 (1.8 - 5.6) | 2.9 - 3.5 | 3.3 ± 1.7 (1.4 - 6.4) | 3.0 ± 1.6 (1.8 - 2.6) | >0.05 |
| Prothrombin index (%) | 80-110 | 22 | 94 ±23 (18 - 127) | 86 - 102 | 72 ± 25 (35 - 96) | 79 ± 14 (66 - 95) | **<0.05** |
| Glucose (mmol/L) | 3.6-6.2 | 45 | 7.5 ± 4.8 (3.2 - 26.2) | 5.7 - 9.3 | 8.8 ± 3.7 (4.7 - 14.3) | 7.4 ± 2.6 (4.1 -10.8) | >0.05 |
| BUN (mmol/L) | 1.7-8.3 | 12 | 5.5 ± 2.1 (2.4 - 10.4) | 4.5 - 6.5 | 5.1 ± 1.8 (3.0 - 6.5) | 4.2 ± 0.9 (3.5 - 4.8) | >0.05 |
| Creatinine (µmol/L) | 44.2-134 | 0 | 72.9 ± 21.3 (30 - 118) | 63 - 83 | 76.8 ± 26.6 (58 - 116) | 105 ± 4 (102 -108) | >0.05 |

≠N – out of reference range; SD – standard deviation; WBC – white blood cells; ASAT – aspartate aminotransferase; ALAT – alanine aminotransferase; GGT – gamma glutamyl transferase; BUN – blood urea nitrogen

The severity was assessed as mild in 42%, moderate in 36% and 21% of the cases had a severe course of the disease. Only one of the severe cases had not co-morbidity. About the duration of the clinical syndromes, it is worthy of note that the jaundice was protracted (median six days after hospital admission and in one of the cases – elder patient – to 42 days). All of the patients were successfully treated with glucose infusions, hepatoprotective drugs and

vitamins (from 5 to 42 days, mean 10 days).

After a review of the literature, we performed a comparative analysis of demographic, epidemiological, clinical characteristics and laboratory parameters in four foreign and two Bulgarian series of VHE – our presented here analysis and the study of Pishmisheva M [21]. The results of this comparative analysis have been shown in table 2.

**Table 2.** Comparative analysis of demographic, epidemiological, clinical and laboratory characteristics of VHE in different series

| Variables | Mansuy et al. [11] | Takahashi et al. [13] | Woolson et al. [16] | Said et al. [27] | Pishmisheva [21] | Gancheva | **P** |
|---|---|---|---|---|---|---|---|
| Target group and subjects - n | Hospitalized 62 | Hospitalized 207 | Hospitalized 106 | Cruize outbreak 33 | Hospitalized 139 | Hospitalized 33 | - |
| Diagnosis - % Anti-HEV IgM (+) -1; RT PCR-HEV RNA (+) - 2 | *2 -* 100% | *1 -* 99.5% *2 -* 100% | *1 -* 91% *2 -*75% | *1 –* 100%; *2 -* 9% | *1 -* 100%; *2 -* 9% | *1 -* 100% | - |
| Genotype | 55/62 – Genotype 3 – 100% | Genotype 3/4 (*n - 128*) Genotype 4 (*n = 74*) | 57/78 – Genotype 3 – 100% | Genotype 3 | 7/15 – Genotype 3 – 100% | - | - |
| Country | France | Japan | Southeastern England | UK citizens | Bulgaria | Bulgaria | - |
| Period | 2003-2007 | 1993-2012 | 1999-2013 | 2008 | 2014-2017 | 2016-2019 | - |
| Comorbidity % | 32.3 | ? | ? | ? | **81** | **79** | **<0.05** |
| Mortality rate % | 1.6 | 0 | 3.8 | 0 | **5.7** | 0 | **<0.025** |
| Mean age/ median (years – range) | Male –58 (20-82) Female – 48 (25-77) | 56.8/- (18-86) | -/63.5 (18-92) | 68 (22-92) | 57/ | 59/62 (16-77) | >0.05 |
| Age >50 years % | or elder | 70 | ? | 90 | 76 | 67 | >0.05 |
| Male gender % | 66 | 80 | 76 | 76 | 71 | 55 | **<0.05** |
| Urban residents % | 42 | ? | ? | ? | **63** | **79** | **<0.05** |
| Seasonality | Without variability | ? | March, July | March | Feb. – March June - August | March - April | NA |
| Travelling abroad % | 3.2 | 3.9 | 12.3 | 100 | ? | 6 | NA |
| Blood manipulation% | 3.2 | ? | ? | - | ? | 24 | NA |
| Fever % | 27.4 | - | 11 | - | 22 | 15 | >0.05 |
| Fatigue % | 40.3 | - | 34 | 33 | **87** | **94** | **<0.05** |
| Headache % | 9.7 | - | ? | - | **24** | 3 | **<0.05** |
| Drowsiness % | ? | - | 34 | - | **40** | 6 | **<0.05** |
| Abdom. discomfort % | ? | - | NA | 15 | **40** | **39** | **<0.05** |
| Abdominal pain % | 11.3 | - | 26 | 15 | 40 | 36 | >0.05 |
| Nausea % | 9.7 | - | 29 | 33 | **42** | **58** | **<0.05** |
| Vomiting % | ? | - | 29 | 21 | 28 | 24 | >0.05 |
| Loss of appetite % | 8.1 | - | 23 | 33 | 71 | 76 | >0.05 |
| Itching % | ? | - | 7 | - | **31** | 12 | **<0.005** |
| Arthralgia % | **21** | - | 14 | - | 8 | 9 | >0.05 |
| Myalgia % | - | - | 7 | - | - | 9 | >0.05 |
| Jaundice % | 68 | - | 58 | 21 | **87** | **79** | **<0.05** |
| Rash % | 3.2 | - | 3 | - | 7 | 0 | >0.05 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Hepatomegaly % | ? | - | ? | ? | **96** | **100** | **<0.05** |
| Splenomegaly % | ? | - | ? | ? | 27 | **67** | **<0.0005** |
| Neurol. disorders % | ? | - | 8 | ? | 0 | 0 | >0.05 |
| Hemoglobin (g/L) | - | - | 143 (111–188) | - | ↓ - 40% | ↓ - 12%; 131 ±17 (90 - 165) | **<0.0005** |
| WBC (cells x $10^9$ /L) | - | - | 6.7 (2.4–22.9) | - | ↓ - 5%; ↑ - 16% | ↓ - 12%; 8.4 ±4.2 (4.4 – 25.3) | >0.05 |
| Platelets (cells x $10^9$ /L) | - | - | 11%; 226 (40–538) | - | ↓ - 23% | ↓ - 18%; 229 ±85 (52 - 419) | >0.05 |
| Total bilirubin (µmol/L) | 5–30N | 6.9 ± 8.2; 10.2 ± 7.9 mg/dL | /50 (3–417) | ↑ - 91% | ↑ - 87%; 108 | ↑ - 82%; 94 ± 91 (6.7 - 378) | >0.05 |
| Direct bilirubin (µmol/L) | - | - | - | - | ↑ - 87% | ↑ - 96%; 78 ± 68 (3.8 - 374) | >0.05 |
| ASAT (IU/L) | 1.5–151N | 2146 ± 2226 2503 ± 2049 | ? | ↑ - 67% | 842 | ↑ - 100%; 812 ± 629 (67 - 3003) | >0.05 |
| ALAT (IU/L) | 4–150N | 2310 ± 1800 2979 ± 1887 | /1107 (27–6357) | ↑ - 100% | 1238 | ↑ - 100%; 1327 ± 790 (80 - 3516) | >0.05 |
| GGT (IU/L) | - | - | ? | - | 524 | ↑ - 100%; 358 ± 221 (59 - 922) | NA |
| Alkaline phosphatase (IU/L) | - | - | /218 (57–736) | ↑-67% | 397 | ↑ - 90%; 269 ± 165 (76 - 782) | NA |
| Total protein (g/L) | - | - | - | - | ↓ - 22% | ↓ - 4%; 69.6 ±5.2 (59 - 77) | **<0.0005** |
| Albumins (g/L) | - | - | /40 (25–48) | - | ↓ - 20% | ↓ - 12%; 40.6 ± 5.0 (31 - 49.1) | >0.05 |
| Fibrinogen (g/L) | - | - | - | - | - | ↓ - 3%; 3.2 ± 0.8 (1.8 - 5.6) | NA |
| Prothrombin index (%) | - | <60% - 19.5% <40% - 12.5% | - | - | ↓ - 16% | ↓ - 22%; 94 ±23 (18 - 127) | >0.05 |
| Glucose (mmol/L) | - | - | - | - | - | ↑ - 45%; 7.5 ± 4.8 (3.2 - 26.2) | NA |
| BUN (mmol/L) | - | - | - | - | ↑ - 19% | ↑ - 12%; 5.5 ± 2.1 (2.4 - 10.4) | >0.05 |
| Creatinine (µmol/L) | - | - | /78 (34–633) | - | **↑ - 21%** | ↑ - 0%; 72.9 ± 21.3 (30 - 118) | **<0.0005** |

↑ – above the reference range; ↓ – below the reference range; WBC – white blood cells; ASAT – aspartate aminotransferase; ALAT – alanine aminotransferase; GGT – gamma glutamyltransferase; BUN – blood urea nitrogen

**DISCUSSION:**

The analysis of the demographic characteristic of patients in our series revealed a prevalence of age of cases over sixty years (55%), and 67% are over 50 years. This correlates with other series – 70%, 90% and 76% according to Takahashi et al. (2014) Said et al. (2009) and Pishmisheva (2018), respectively (*P* >0.05) [13, 21, 27]. According to Aspinall et al. (2017), the highest incidence of VHE also is observed in people over fifty years [12]. A study from Romania reported that 28% HEV-positive were in the age group of 45-65 years) [28]. According to the study of Eker et al. (2009), the mean age of patients with VHE was 50.9 ± 16.8 years [29]. In a study from Albania, 35% of HEV-positive cases were in people over 50 years [30].

Males are significantly prevalent in all of the mentioned series in the comparative analysis indifference than our study (*P* <0.05). This correlates with the study of Aspinall et al. (2017), in which males are 61 – 69%) [12]. In Bulgarian studies for HEV the gender distribution male/female is 80.0/20.0%) [19, 20, 23]. The data reported from Romania [28] and Turkey [29] are opposite (male/female – 40/60% and 21.4/78.6%, respectively).

Co-morbidity is significantly higher in our study and other Bulgarian series of Pishmisheva [21], comparing with Mansuy et al. [11] (*P* <0.05).

Most of our cases are registered during March and April, and a similar seasonality is observed in some of the compared series [16, 21]. A cruise outbreak studied by Said et al. (2009) was also reported during March [27].

About the clinical characteristics, jaundice and hepatomegaly were registered in all our cases (79% and 100%, respectively), and fatigue also is common (94%). A similar prevalence of these symptoms (87%, 96%, and 87%, respectively) is reported in the study of Pishmisheva (*P* >0.05) [21]. But in other series, the respective prevalence is significantly lower (jaundice in 58% and fatigue in 34%, according to Woolson et al.; 68% and 40%, respectively, according to Mansuy et al.) (*P* <0.05) [11, 16]. Headache (24%) and drowsiness (40%) are significantly commonest in study of Pishmisheva (*P* <0.05) [21]. Loss of appetite also is common in our series (76%), and similar prevalence is registered in the study of Pishmisheva (71%) [21] (*P* >0.05); nausea – in 58% and 42%, respectively (*P* <0.05). In other compared series, the prevalence of the mentioned symptoms is significantly lower (*P* <0.05) [11, 16, 27]. Splenomegaly is registered in 67% of our cases (*P* <0.05). The possible explanation of these discrepancies is the variable severity of cases in different series.

About laboratory characteristics, anaemia is registered in 12% of our study and in 40% according to Pishmisheva (*P* <0.0005) [21]. There are no significant differences in other parameters of the blood count. Total bilirubin level is increased in 82% of our patients and according to Said (2009) and Pishmisheva (2018) – in 91% and 87%, respectively (*P* >0.05) [21, 27]. The aminotransferases activity is increased in all of our cases, but according to Said et al. (2009), ASAT is increased in 67% of their cases (ALAT – in 100%) [27]. GGT is moderately increased in all our patients (100%) and alkaline phosphatase – in 90%. The total protein is decreased only in 4% of our cases, contrasting to the study of Pismisheva (22%) (*P* <0.0005) and albumin level is decreased in 12% and 20% of the cases, respectively (*P* >0.05) [21]. The lack of analogous data for the remainder compared series eliminates the possibility for exact general assessment.

**CONCLUSIONS:**

The clinicians should consider VHE in the diagnostic process of patients with jaundice from an unknown origin. Precise epidemiological history also suggests a possible diagnosis. The disease affects mainly older ages, and the jaundice is protracted.

**REFERENCES:**

1. EASL Clinical Practice Guidelines on hepatitis E virus infection. European Association for the Study of the Liver (EASL). *J of Hepatol.* 2018 June; 68:1256-71. [PubMed]

2. Dalton H, Bendall R, Ijaz S, Banks M. Hepatitis E: an emerging infection in developed countries. *Lancet Infect Dis.* 2008 Nov;8-11:698-709. [PubMed]

3. Kamar N, Bendall R, Legrand-Abravanel F, Xia NS, Ijaz S, Izopet J, et al. Hepatitis E. *Lancet.* 2012 Jun 30; 379(9835):2477-88. [PubMed]

4. Khuroo MS. Study of an epidemic of non-A, non-B hepatitis. Possibility of another human hepatitis virus distinct from post-transfusion non-A, non-B type. *Am J Med.* 1980 Jun; 68(6):818-24. [PubMed]

5. Mohammad S Khuroo, Mehnaaz S Khuroo, and Naira S Khuroo. Hepatitis E: Discovery, global impact, control and cure. *World J Gastroenterol.* 2016 Aug 21;22(31):7030-45. [PubMed]

6. Balayan M, Andjaparidze A, Savinskaya S, Ketiladze E, Braginsky D, Savinov A, et al. Evidence for a virus in non-A, non-B hepatitis transmitted via the fecal-oral route. *Intervirology.* 1983;20(1):23-31. [PubMed]

7. Reyes G, Purdy M, Kim J, Luk K, Young L, Fry K, et al. Isolation of a cDNA from the virus responsible for enterically transmitted non-A, non-B hepatitis. *Science.* 1990 Mar 16; 247(4948):1335-9. [PubMed]

8. Pishmisheva M, Baymakova M, Golkocheva-Markova E, Kundurzhiev T, Pepovich R, Popov GT, et al. First serological study of hepatitis E virus infection in pigs in Bulgaria. *Comptes rendus de l'Academie bulgare des Sciences.* 2018;71(7):1001-8. [Crossref]

9. Hoofnagle J, Nelson K, Purcell R. Hepatitis E. *N Engl J Med.* 2012 Sep 27;367(13):1237-44. [PubMed]

10. Waterborne Outbreaks of Hepa-

titis E: Recognition, Investigation and Control. World Health Organization. July 2014. [Internet]

11. Mansuy J, Abravanel F, Miedouge M, Mengelle C, Merviel C, Dubois M, et al. Acute hepatitis E in south-west France over a 5-year period. *J of Clin Virol.* 2009 Jan;44(1):74-7. [PubMed]

12. Hepatitis E in the EU/EEA, 2005-2015: Baseline assessment of testing, diagnosis, surveillance and epidemiology. Stockholm (Sweden): ECDC. Jul 11 2017. [Internet]

13. Takahashi M, Okamoto H. Features of hepatitis E virus infection in humans and animals in Japan. *Hepatol Res.* 2014 Jan;44(1):43-58. [PubMed]

14. Mclean BN, Gulliver J, Dalton HR. Hepatitis E virus and neurological disorders. *Pract Neurol.* 2017 Aug; 17(4):282-8. [PubMed]

15. Denner J. Hepatitis E virus (HEV) - The Future. *Viruses.* 2019 Mar 13;11(3):251. [PubMed]

16. Woolson KL, Forbes A, Vine L, Beynon L, McElhinney L, Panayi V, et al. Extra-hepatic manifestations of autochthonous hepatitis E infection. *Aliment Pharmacol Ther.* 2014 Dec;40(11-12):1282-91. [PubMed]

17. Pepovich R, Baymakova M, Pishmisheva M, Marutsov P, Pekova L, Tsachev I. Current knowledge on Hepatitis E virus infection. *Vojnosanit Pregl.* 2019; 76(7):733-9. [Crossref]

18. Teoharov P, Tiholova M, Draganov P, Lilyanova V, Ivanova R, Varleva T, et al. First cases of hepatitis E virus infection in Bulgaria. *Infectology.* 1995;32:17-8. [in Bulgarian]

19. Teoharov P, Kevorkyan A, Raycheva R, Golkocheva-Markova E, Trandeva-Bankova D, Andonov A. Data on the prevalence of hepatitis E virus in Bulgaria. *Comptes rendus de l'Academie bulgare des Sciences.* 2014 Oct; 67(10):1427-32. [Internet]

20. Dikov I, Popov G, Plochev K, Baymakova M. [Hepatitis E virus infection in Bulgaria.] [in Bulgarian] *Bulg Hepatogastroenterology (Sofia).* 2012; 14:37-40.

21. Pishmisheva M. [Clinical and epidemiological aspects of acute viral hepatitis E infection.] [dissertation] Medical University of Plovdiv. 2018. [in Bulgarian]

22. Baymakova M, Popov G, Pepovich R, Tsachev I. Hepatitis E virus Infection in Bulgaria: A Brief Analysis of the Situation in the Country. *Open Access Maced J Med Sci.* 2019 Jan 25;7(3):458-60. [PubMed]

23. Petrov A, Stoycheva M, Vatev N, Boev I. [Viral hepatitis E in Plovdiv district: epidemiological, clinical and biochemical characteristics.] [in Bulgarian] *Sci Infectol Parasitol.* 2015; 6(1):29-31. [Internet]

24. Baymakova M, Sakem B, Plochev K, Popov G, Mihaylova-Garnizova R, Kovaleva V, et al. Epidemiological characteristics and clinical manifestations of hepatitis E virus infection in Bulgaria: a report on 20 patients. *Srp Arh Celok Lek.* 2016 Jan-Feb;144(1-2):63-8. [PubMed]

25. Stoykova Z, Ivanova L, Tsaneva-Damyanova D, Kostadinova T. [Hepatitis E virus infection in North-eastern Bulgaria.] *Medical Review.* 2017; 53(3):30-4. [in Bulgarian]

26. Bruni R, Villano U, Equestre M, Chionne P, Madonna E, Trandeva-Bankova D, et al. Hepatitis E virus genotypes and subgenotypes causing acute hepatitis, Bulgaria, 2013-2015. *PLoS One.* 2018 Jun 7;13(6): e0198045. [PubMed]

27. Said B, Ijaz S, Kafatos G, Booth L, Thomas HL, Walsh A, et al. Hepatitis E outbreak on cruise ship. *Emerg Infect Dis.* 2009 Nov;15(11):1738-44. [PubMed]

28. Anita A, Gorgan L, Anita D, Oslobanu L, Pavio N, Savuta G. Evidence of hepatitis E infection in swine and humans in the East Region of Romania. *Int J Infect Dis.* 2014 Dec; 29:232-7. [PubMed]

29. Eker A, Tansel O, Kunduracilar H, Tokuc B, Yulugkural Z, Yuksel P. [Hepatitis E virus epidemiology in adult population in Edirne province, Turkey.] [in Turkish] *Mikrobiyol Bul.* 2009 Apr;43(2):251-8. [PubMed]

30. Kondili L, Chionne P, Porcaro A, Madonna E, Taffon S, Resuli B, et al. Seroprevalence of hepatitis E virus (HEV) antibody and the possible association with chronic liver disease: a case-control study in Albania. *Epidemiol Infect.* 2006 Feb;134(1):95-101. [PubMed]

**Address for correspondence:**
Galya Ivanova Gancheva
Clinic of Infectious Diseases, University Hospital,
8A, Georgi Kochev Str., Pleven 5800, Bulgaria
E-mail: galya_gancheva@abv.bg