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Retrospective Cross-Sectional Study on Chronic Hepatitis C in Estonia, Latvia, Lithuania, and Ukraine: Virus, Patient, and Disease Characteristics in Patients under Care (RESPOND-C Study)

Ligita Jančorienė [1], Baiba Rozentāle [2], Ieva Tolmane [2,3], Agita Jēruma [2,4], Riina Salupere [5], Arida Buivydienė [6,7], Jonas Valantinas [6,7], Limas Kupčinskas [8,*], Jolanta Šumskienė [8], Eglė Čiupkevičienė [8,9] Arvydas Ambrozaitis [1], Olga Golubovska [10], Larysa Moroz [11], Robert Flisiak [12] and Borys Bondar [13,]

[1] Clinic of Infectious Diseases and Dermatovenerology, Institute of Clinical Medicine, Medical Faculty, Vilnius University, Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania
[2] Latvian Centre of Infectious Diseases, Riga East Clinical University Hospital, Riga, Latvia
[3] Faculty of Medicine, University of Latvia, Riga, Latvia
[4] Faculty of Medicine, Riga Stradins University, Riga, Latvia
[5] Tartu University Hospital, University of Tartu, Tartu, Estonia
[6] Clinic of Gastroenterology, Nephrourology and Surgery, Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania
[7] Centre of Hepatology, Gastroenterology and Dietetics, Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania
[8] Department of Gastroenterology, Lithuanian University of Health Sciences, Kaunas, Lithuania
[9] Health Research Institute, Faculty of Public Health, Lithuanian University of Health Sciences, Kaunas, Lithuania
[10] O.O. Bogomolets National Medical University, Kyiv, Ukraine
[11] National Pirogov Memorial Medical University, Vinnytsya, Ukraine
[12] Department of Infectious Diseases and Hepatology, Medical University of Bialystok, Bialystok, Poland
[13] AbbVie Biopharmaceuticals GmbH, Kyiv, Ukraine
* Correspondence: limas.kupcinskas@lsmu.lt

Abstract: *Background and objectives:* Since 2013, highly effective direct-acting (DAA) chronic hepatitis C (CHC) antiviral therapy became available, which has cure rates of over 95%. For choice of optimal CHC treatment, assessment of hepatitis C virus (HCV) genotype (GT) and liver fibrosis stage are necessary. Information about distribution of these parameters among CHC patients in Baltic states and especially in Ukraine is scarce. This study was performed to obtain epidemiologic data regarding CHC GT and fibrosis stage distribution for better planning of resources and prioritization of patients for DAA drug treatment according to disease severity in high-income (Baltic states) and lower-middle income (Ukraine) countries. *Materials and Methods:* This was an epidemiologic, retrospective, cross-sectional study that included 1451 CHC patients. Demographic and disease information from medical charts was collected for each patient during a single visit. *Results:* Most frequent suspected mode of viral transmission was blood transfusions (17.8%), followed by injection drug use (15.7%); however, in 50.9% of patients exact mode of transmission was not clarified. In Ukraine (18.4%) and Estonia (26%) transmission by the injection drug use was higher than in Lithuania (5%) and Latvia (5.3%). Distribution of HCV GT among patients with CHC was as follows: GT1 - 66.4%; GT3 - 28.1; and GT2 - 4.1%. The prevalence of GT1 was the highest in Latvia (84%), and the lowest in Ukraine (63%, p<0.001). Liver fibrosis stages were distributed as follows: F0 - 12.2%, F1 - 26.3%, F2 - 23.5%, F3 – 17.1% and F4 - 20.9%. Cirrhosis (F4) was more prevalent in Lithuanian patients (30.1%) than in Estonians (8.1%, p <0.001). *Conclusions:* This study contributes to the knowledge of epidemiologic characteristics of HCV infection in the Baltic states and Ukraine. The data regarding the patterns of HCV GT and fibrosis stage distribution will be helpful for the development of national strategies to control HCV infection in the era of DAA therapy.

Keywords: Baltic states; chronic hepatitis C; epidemiology; hepatitis C virus; genotype; Ukraine

1. Introduction

An estimated 58 million people have chronic hepatitis C virus infection, with about 1.5 million new infections occurring per year. The highest burden of disease is in the Eastern Mediterranean Region and European Region, with 12 million people chronically infected in each region [1,2]. In the South-East Asia Region and the Western Pacific Region, an estimated 10 million people in each region are chronically infected. Nine million people are chronically infected in the African Region and 5 million the Region of the Americas. In the European Region of World Health Organization (WHO), the prevalence of HCV is higher outside the EU/EFTA countries, and many infected individuals are not aware of their infection [3]. HCV is most commonly transmitted via the blood. Thus, intravenous (as well as intranasal) drug users, dialysis patients, and those undergoing tattooing or manicure and pedicure services are at risk of infection [4,5]. In rare cases, HCV can also be transmitted vertically from a mother to a child, and the virus can also be spread through sexual intercourse [4,5]. Of those with chronic HCV infection, the risk of cirrhosis ranges from 15% to 30% within 20 years. [6,7]. Six major genotypes of HCV have been defined, with more than 50 subtypes described; the most common subtypes are 1a, 1b, 2a, and 2b [8]. Determination of HCV genotype and liver fibrosis stage is essential to making decisions about treatment, as the regimens, dosing, and duration of therapy vary across the genotypes [9]. Pan-genotypic DAAs remain expensive in many high- and upper-middle-income countries. Access to HCV treatment is improving but remains too limited. Of the 58 million persons living with HCV infection globally in 2019, an estimated 21% (15.2 million) knew their diagnosis, and of those diagnosed with chronic HCV infection, around 62% (9.4 million) persons had been treated with DAAs by the end of 2019.

The prevalence of HCV infection is relatively high in the Baltic countries. In Estonia, it affects 1.5% to 2.0% of the population [10], in Latvia, 2.4% [10], and in Lithuania, 1.7% [12]. In Ukraine, official statistics or registries for HCV infection are scarce; however, the estimated prevalence of infection is assessed as very high - 3.5% [13].

In 2016, the World Health Assembly passed a resolution to eliminate viral hepatitis as a public health threat by 2030 [14]. Safe and effective drugs direct-acting antivirals (DAA) are now available; however, most patients remain unaware of their infection, which may be recognized only in late stages when the complications have occurred. Furthermore, the high cost of new drugs requires prioritization in their allocation. Thus, identifying patients at high risk of dying from CHC and ensuring appropriate treatment is a health care challenge, especially in lower-income countries. WHO issued the new guidelines for treating CHC based on a patient's clinical history as well as the genotype of HCV [15]. WHO now recommends that testing, care and treatment for persons with chronic hepatitis C infection can be provided by trained non-specialist doctors and nurses.

Given the relatively high prevalence of HCV infection in the Baltic countries and Ukraine, as well as scarce clinical data regarding disease progression and treatment, this study aimed to obtain epidemiologic data regarding HCV GT and fibrosis stage distribution for better planning of health care resources to achieve WHO goal to eliminate hepatitis C infection till 2030 in high-income Baltic countries and lower middle-income country Ukraine.

2. Materials and Methods

2.1. Study Design and Sample

This was an epidemiologic study with a retrospective, cross-sectional, and multi-center design. Centers from different geographical regions of Ukraine, Estonia, Latvia, and Lithuania were selected to participate in the study based on the following selection criteria: selected centers were both inpatient and outpatient reference centers with experience in the treatment of CHC and current access to patients with HCV infection. Centers also had to have the ability to conduct the study following applicable legal and regulatory requirements as well as to perform data entry via an online electronic Case Report Form (e-CRF). Centers had to represent the estimated number of patients in rural or urban areas. Altogether 15 centers (8 in Ukraine, 1 in Latvia, 3 in Lithuania, and 3 in Estonia) were involved in the study.

Study enrollment was planned for approximately 1450 patients (100 from Estonia, 150 from Latvia, 200 from Lithuania, and 1000 from Ukraine). Study investigators enrolled patients until the sample had reached these predefined limits. To reduce selection bias at the patient level, all patients with HCV infection who attended a routine visit at each participating center within the past 6 months

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before study initiation were identified as possible eligible patients for the study. Furthermore, patients had to fulfill the following selection criteria: diagnosis of chronic HCV infection confirmed with a positive HCV-RNA test, defined HCV GT, and age ≥18 years. All patients had to provide patient authorization (consent) for use/disclosure of data. Patients with a diagnosis of acute hepatitis C were excluded from data collection.

In total, 1490 patients were enrolled in the study. Due to missing data, 39 (2.6%) of patients were excluded from the study. Therefore, data of 1451 patients were analyzed (100 from Estonia, 150 from Latvia, 201 from Lithuania, and 1000 from Ukraine.

2.2. Data Collection and Variables

Information was collected from patient's medical documentation on a pre-established e-CRF at a single time point for each patient. Demographic data included age at the time of the study, gender, geographic location (country), duration of HCV infection, GT classification, alcohol consumption, and substance use. Patients were asked about their alcohol consumption habits, which were classified as 'Yes', if they consumed any alcoholic drink, or No, if they did not. Regarding substance use, patients were classified as former drug users, active drug users and those who had never used drugs. Patients who failed to provide an answer about their substance or alcohol consumption were marked as "Unknown." Collected clinical data were fibrosis stage, hepatocellular carcinoma (HCC) status, and infection characteristics.

GTs were grouped as follows: GT1 (overall and separately as GT1a, GT1b, and GT1 undefined), GT2, GT3, GT4, GT5, GT6, GT other, or GT mixed.

Liver fibrosis stage was most frequently based on histology results obtained from liver biopsy specimen analysis and/or liver stiffness measurement by transient elastography (TE) using FibroScan® model 402 with M probe (Echosens, Paris, France). According to the manufacturer's recommendations, only TE results obtained with 10 valid measurements and a success rate of at least 60% (with <30% interquartile range) were considered reliable. Fibrosis stages were categorized using the METAVIR scoring system as follows: F0 - no fibrosis; F1 - portal fibrosis without septa; F2 - portal fibrosis with few septa; F3 - numerous septa without cirrhosis; and F4 - cirrhosis.

In this study, the following modes of infections were assessed: unsafe injection (e.g., drug use, needle stick injury), blood transfusion, hemodialysis, organ transplantation, dental procedures, other invasive procedures (e.g., tattooing/body piercing), unknown, and other.

As HCV infection shares a similar mode of transmission with other viruses, patients were also categorized according to their co-infection status with human immunodeficiency virus (HIV) infection.

2.3. Data Analysis

The categorical variables were presented as proportions and compared using a χ^2 test and Z-test with Bonferroni correction. Bonferroni corrected alpha level was set at 0.008 when proportions between 4 countries were compared using Z-test (0.05/6 pairwise comparisons). Statistical analysis was performed using SAS 9.2 for Windows (SAS Institute, Cary, NC, USA).

2.4. Ethical Statement

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and approval to conduct the study was issued by the Ethics Committee of Latvia, protocol N 19-A/15 on 06.08.2015; the Lithuanian Bioethics Committee, protocol NL-15-07/1; and the Tallinn Medical Researches Ethics Committee, protocol N 1139 on 17.09.2015. In Ukraine, the legislation does not require ethical approval for non-interventional studies.

3. Results

3.1. Demographics and General Characteristics

The study population included 845 (58.2%) men and 606 (41.8%) women. The mean age of patients was 43.9 (SD 11.7) years (range 18.0–82.0 years). The general characteristics of the study population are shown in Table 1.

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Table 1. General characteristics of the study participants.

Characteristics	Ukraine (N=1000)		Estonia (N=100)		Latvia (N=150)		Lithuania (N=201)		Total (N=1451)		P-value
	n	%	n	%	n	%	n	%	n	%	
Male	613	61.3	59	59.0	69	46.0	104	51.7	845	58.2	<0.001
Female	387	38.7	41	41.0	81	54.0	97	48.3	606	41.8	
Drug abuse											
Former drug user	171	17.1	24	24.0	11	7.3	10	5.0	216	14.9	
Active drug user	20	2.0	0	0.0	0	0.0	1	0.5	21	1.5	<0.001
Never used	772	77.2	70	70.0	137	91.4	188	93.5	1167	80.4	
Unknown	37	3.7	6	6.0	2	1.3	2	1.0	47	3.2	
Alcohol consumption											
Yes	175	17.5	19	19.0	5	3.4	30	14.9	229	15.8	<0.001
No	757	75.7	67	67.0	143	95.3	170	84.6	1137	78.3	
Unknown	68	6.8	14	14.0	2	1.3	1	0.5	85	5.9	
Suspected mode of infection											
Injection drug use	184	18.4	26	26.0	8	5.3	10	5.0	228	15.7	
Blood transfusion	156	15.6	21	21.0	28	18.7	53	26.4	258	17.8	<0.001
Dental procedures	172	17.2	2	2.0	51	34.0	2	1.0	227	15.6	
Unknown	488	48.8	51	51.0	63	42.0	136	67.6	738	50.9	
Duration of HCV infection											
≥0 and <3 years	410	41.0	22	22.0	50	33.4	78	38.8	560	38.7	
≥3 and <5 years	211	21.2	19	19.0	17	11.3	32	15.9	279	19.2	<0.001
≥5 and <10 years	270	27.0	26	26.0	44	29.3	52	25.9	392	27.0	
≥10 years	108	10.8	33	33.0	39	26,0	39	19.4	219	15.1	
Fibrosis stage											
F0	122	16.6	6	6.9	12	8.5	1	0.5	141	12.2	
F1	178	24.4	37	42.5	58	40.8	31	16.1	304	26.3	
F2	171	23.3	24	27.6	21	14.8	55	28.4	271	23.5	<0.001
F3	113	15.4	13	14.9	24	16.9	48	24.9	198	17.1	
F4 (cirrhosis)	149	20.3	7	8.1	27	19.0	58	30.1	241	20.9	
Total	733	100	87	100	142	100	193	100	1155	100	
HIV and/or HBV co-infection status											
Yes	125	12.5	24	24.0	0	0.0	0	0.0	149	10.3	0.001
No	875	87.5	76	76.0	150	100	201	100	1302	89.7	
HCC status											
Yes	4	0.4	1	1.0	3	2.0	4	2.0	12	0.8	<0.001
No	842	84.2	82	82.0	120	80.0	187	93.0	1231	84.9	
Unknown	154	15.4	17	17.0	27	18.0	10	5.0	208	14.3	

Abbreviations: HCC; hepatocellular carcinoma; HCV, hepatitis C virus.

Substance abuse was uncommon among study participants. There were 20 (2%) active drug users in Ukraine and 1 (0.5%) in Lithuania. The highest proportion of former drug users was found in Estonia (24%) and Ukraine (17.1%). The prevalence of alcohol consumption varied from 3.4% in Latvia to 19% in Estonia. The suspected mode of infection differed between countries. In Lithuania, the main route of HCV transmission was blood transfusion (26.4%). Injection drug use was most frequently recorded in Estonia (26%) and Ukraine (18.4%). Even 34% of Latvian patients were suspected being infected via dental procedures. The route of transmission was not defined in 738 (50.9%) patients.

The highest proportion of patients with a disease duration of 10 years and more was in Estonia (33%). In all countries except Estonia, the duration of disease in most patients was up to 3 years. HIV and/or HBV co-infection was identified in 125 (12.5%) patients in Ukraine and 24 (24%) in Estonia.

Overall, comorbidities were reported in 30.7% of patients (445/1451). Other liver diseases accounted for 55.5% of all comorbidities (208/445 patients), and they were the most frequent conditions in every country. Other chronic infectious diseases made up 16.3% of comorbidities (61/445) and diseases of the circulatory system - 11.5% (43/445) (data are not shown).

In all countries except Lithuania, the highest proportion of patients had a F1 stage of liver fibrosis. Almost one third (30.1%) of Lithuanian patients were diagnosed with liver cirrhosis (F4). HCC was found in 4 (0.4%) patients in Ukraine and 8 (1.8%) patients in Baltic countries.

3.2. Genotype Distribution

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As shown in Table 2, the overall pattern of HCV GT distribution was similar among all studied countries. In general, GT1 was most common, accounting for 963 of all infections (66.4%), followed by GT3 (n=408; 28.1%). Only small percentages of GT2, mixed GT, or GTs not further classified were reported (Table 2). GTs 4, 5, and 6 were not identified among the study participants. Subtype 1b accounted for 76.4% (765/963) of all GT1 infections, and 94.3% (765/811) of all subtype-defined GT1 infections.

Table 2. HCV genotype distribution according to geographic location.

Country	Genotypes								
	GT1 All subtypes, n (%)	GT1 Subtype*			GT2, n (%)	GT3, n (%)	Other than GT1–6, n (%)	Mixed GTs, n (%)	P-value
		GT1 Un-defined, n (%)	GT1a, n (%)	GT1b, n (%)					
Ukraine n=1000	630 (63.0%)	88 (14.0%)	19 (3.0%)	523 (83.0%)	45 (4.5%)	317 (31.7%)	2 (0.2%)	6 (0.6%)	<0.001
Latvia n=150	126 (84.0%)	51 (40.5%)	1 (0.8%)	74 (58.7%)	2 (1.3%)	21 (14.0%)	0	1 (0.7%)	
Lithuania n=201	140 (69.7%)	13 (9.3%)	23 (16.4%)	104 (74.3%)	10 (5.0%)	45 (22.3%)	0	6 (3%)	
Estonia n=100	67 (67.0%)	0	3 (4.5%)	64 (95.5%)	3 (3.0%)	25 (25.0%)	0	5 (5.0%)	
Total n=1451	963 (66.4%)	152 (15.8%)	46 (4.8%)	765 (79.4%)	60 (4.1%)	408 (28.1%)	2 (0.1%)	18 (1.3%)	

Abbreviations: GT, genotype; HCV, hepatitis C virus. * Percentages of subtypes within GT1 are shown.

Despite predominance of GT1 in all studied countries, some regional differences in GT distribution have been found (Table 2). The highest proportion of GT1 was observed in Latvia – 84%. ($p<0.001$ vs Ukraine; $p=0.001$ vs Lithuania and $p= 0.002$ vs Estonia). At the same time, the proportion of GT3 in Latvia was the lowest – 14% ($p<0.001$ vs Ukraine, $p=0.040$ vs Lithuania and $p=0.034$ vs Estonia).

Some variations with respect to GT predominance depending on diseases characteristics were identified. GT1 was detected more frequently in those >50 years of age (74.5% vs 62.3%, $p<0.01$), but GT3 was found more often for those aged <50 years (32.9% vs 18.0%, $p<0.01$; data not shown).

GT distribution differed by fibrosis stages (Table 3). The prevalence of GTs was compared in two groups of patients – those with mild liver disease (F0-F1) and those with more advanced disease (F2-F4). The proportion of GT1 among F2-F4 patients (71.8%; 510/710) was significantly higher than in the F0-F1 group (63.1%; 281/445; $p=0.002$). The proportion of GT2 among F2-F4 patients was significantly lower than in the F0-F1 group (2.4% (17/710) vs 6.3% (28/445) respectively; $p=0.002$). GT3 was found equally often in both groups (24.4% and 29.2% respectively).

GT1 was determined more often among patients with than without HIV co-infection (47.7% and 68.5% respectively; $p<0.001$) (Table3). The prevalence of GT1 and GT3 differed between injection drug users and those who assumed blood transfusion was the mode of infection. GT1 was found in 44.3% of injection drug users and in 81.4% patients suspected being infected through blood transfusion ($p<0.001$). Meanwhile, GT3 prevalence in injection drug users was much higher than in those probably infected through blood transfusion (50.9% and 14.0% respectively, $p<0.001$)

Table 3. HCV genotype distribution according to patient characteristics.

Characteristic	Genotypes					
	GT1, n (%)	GT2, n (%)	GT3, n (%)	Other Than GT1–6, n (%)	Mixed GTs, n (%)	P-value
Fibrosis stage						
F0	92 (65.2%)	6 (4.3%)	42 (29.8%)	0	1 (0.7%)	
F1	189 (62.2%)	22 (7.2%)	88 (29.0%)	1 (0.3 %)	4 (1.3%)	
F2	194 (71.6%)	9 (3.3%)	63 (23.3%)	0	5 (1.8%)	0.038
F3	147 (74.3%)	2 (1.0%)	47 (23.7%)	0	2 (1.0%)	
F4 (cirrhosis)	169 (70.2%)	6 (2.5%)	63 (26.1%)	0	3 (1.2%)	
HIV Co-infection status						

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Yes	71 (47.7%)	3 (2.0%)	70 (47.0%)	0	5 (3.3%)	<0.001
No	892 (68.5%)	57 (4.3%)	338 (26.0%)	2 (0.2%)	13 (1.0%)	
Suspected mode of infection						
Injection drug use	101 (44.3%)	5 (2.2%)	116 (50.9%)	0	6 (2.6%)	
Blood transfusion	210 (81.4%)	12 (4.6%)	36 (14.0%)	0	0	
Invasive healthcare mode**	172 (69.4%)	6 (2.4%)	69 (27.8%)	0	1 (0.4%)	<0.001
Other	206 (68.0%)	16 (5.3%)	77 (25.4%)	1 (0.3%)	3 (1.0%)	
Unknown	274 (66.2%)	21 (5.1%)	110 (26.6%)	1 (0.2%)	8 (1.9%)	

Abbreviations: GT, genotype; HCV, hepatitis C virus. * Percentages of subtypes within GT1 are shown. **Invasive healthcare mode includes dental procedures, organ transplantation, and needle stick injuries.

4. Discussion

A better knowledge of HCV infection epidemiology in a particular country, including the distribution of the various GTs, may substantially contribute to effective prevention and treatment of CHC by focusing on people at risk of infection. This study was one of the first to describe the current epidemiologic features of HCV infection in the Baltic countries and Ukraine.

Our study demonstrated that the distribution of the suspected modes of infection varied between countries. The traditional routes of HCV transmission have changed over the last decades. The introduction of screening assays in 1990 reduced the risk of transmitting HCV via blood transfusions [16]. In our study, blood transfusion was reported as the suspected road of infection by 17.8% of patients, more often in Lithuania. Iatrogenic transmission of HCV because of surgical interventions or dental treatment also declined globally [17]. According to our data, only in Latvia dental procedures were recorded as the suspected mode of infection for every third patient. Strict adherence to standard safety procedures is required to prevent iatrogenic transmission of HCV [18].

Injecting drug use is an important risk factor for transmission of HCV [19,20]. The majority of the new infections are related to illicit drug use [20]. This is of particularly high concern, as a large part of drug users is younger than 25 years. More people who inject drugs had HCV than HIV infection [19]. Our study found the highest proportion of former drug users in Estonia and Ukraine. Effective preventive strategies, substance-abuse treatment and access to sterile injection equipment may help to reduce the prevalence of HCV infection among drug users; however, the evidence suggests the suboptimal level of implementation of preventive programmes in Eastern European countries [21].

HCV infection contributes to liver cirrhosis and HCC [6,22]. Due to the asymptomatic nature of HCV infection, the majority of patients are not aware of when they have been infected [23]. HCV infection is frequently diagnosed when it becomes chronic and end-stage liver diseases occur. Our data revealed that every third patient in Lithuania and every fifth in Ukraine and Latvia were diagnosed with liver cirrhosis. HCC was found in 12 (0.8%) patients, more in Baltic countries than in Ukraine. However, even 14.3% of patients were not screened for cancers.

Several studies analyzed the role of HCV genotypes in the prediction of liver disease progression and found that HCV genotype 1b increased the risk of hepatocellular carcinoma [24,25]. Our data demonstrated the high prevalence of GT1 HCV (66.4%) in the Baltic countries and Ukraine. Subtype 1b dominated among all GT1 infections. The distribution of HCV genotypes in our study was consistent with previously reported data from Estonia, Latvia, Lithuania, and Ukraine [26]. The proportion of GT1 was higher in patients from Latvia and older patients in all countries. Previous studies also found that genotype distribution is related to age [27,28]. GT1 was more frequently observed in older age groups. Our data revealed a higher prevalence of GT1 in patients with more advanced liver fibrosis stages. These findings appear to be consistent with previous observations that showed an association between the HCV GT and risk of end-stage liver diseases [24,29]. On the contrary, some other studies demonstrated that GT3 is associated with a higher rate of hepatic steatosis and more rapid progression of liver fibrosis compared to infection with other HCV GTs [30,31]. An increased risk of HCC among GT3 infected individuals than among those with other GTs was reported in the USA and Korea [32,33]. We were not able to analyze the association between HCC and GTs because of the very low number of patients with HCC.

The outcome of a patient depends on an appropriate treatment regimen, which is determined by various factors, including GT. The introduction of DAA has increased the efficacy of HCV infection treatment; however, the GT3 infection showed a lower response compared to other GTs, particularly in treatment-experienced patients and those with liver cirrhosis [34]. European Association for the

Study of the Liver recommends assessment of liver disease severity and HCV genotype determination before therapy. Pan-genotypic HCV drug regimens can be used to treat individuals without identifying their HCV genotype and subtype; however, identifying certain genotypes may be required where drug pricing dictates genotype-specific treatment, also, to optimize treatment regimens [35].

Availability of DAA and treatment with their combinations can cure the majority of HCV-infected patients; however, a high proportion of them remain still undiagnosed and are at risk of developing cirrhosis and HCC [1,2]. Also, some limitations in access to treatment still exist in the countries, particularly in those with lower income [36].

Our study provided new data on the HCV epidemiological situation in the Baltic countries and Ukraine; however, several limitations of the study also should be mentioned. The study design was cross-sectional; therefore, causal links cannot be established. The sample sizes were relatively small, especially in the Baltic countries. A larger sample was studied in Ukraine due to a particular lack of data on the epidemiological situation of HCV in the country. Finally, quite a large proportion of the medical records lacked information on some of the variables analyzed.

5. Conclusion

This study contributes to the knowledge of epidemiologic characteristics of HCV infection in the Baltic states and Ukraine. The data regarding the patterns of HCV GT and fibrosis stage distribution will be helpful for the development of national strategies to control HCV infection in the era of DAA therapy. The national programmes of HCV elimination, which include unlimited access to effective treatment regimes, the nationwide screening programmes to diagnose hidden cases of HCV infection in the population, and appropriate preventive measures to reduce the incidence of HCV infection are urgently needed to achieve the WHO target on HCV elimination by 2030.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approval to conduct the study was issued by the Ethics Committee of Latvia, protocol N 19-A/15 on 06.08.2015; the Lithuanian Bioethics Committee, protocol NL-15-07/1; and the Tallinn Medical Researches Ethics Committee, protocol N 1139 on 17.09.2015. In Ukraine, the legislation does not require ethical approval for non-interventional studies.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to ethical issues.

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