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Prevalence and Risk Factors for Hepatitis C Virus Infection in Vulnerable Populations in Romania: A Population-based Screening from the LIVE(RO)2 Program

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ABSTRACT

Background & Aims: Viral hepatitis C remains one of the leading causes of virus-related morbidity and mortality worldwide, being the main etiological cause of cirrhosis and hepatocarcinoma which transforms it into a global health problem. It investigated the prevalence and risk factors for hepatitis C virus (HCV) infection in Romania.
Methods: This prospective study was conducted between 2021 and 2023 by an extensive national Romanian screening program LIVE(RO)2 of 320,000 participants, most of whom being a part of deemed vulnerable populations. All participants agreed to an informed written consent and potential risk factors for HCV transmission were investigated by questionnaire.
Results: Out of the 320,000 screened individuals, 3,859 were infected with HCV meaning 1.21% prevalence (95%CI: 1.17–1.24). HCV-infected individuals were meanly aged at 65.8 ± 12.93 years, significantly higher as compared to non-infected participants (54.03 ± 16.41 years, p<0.0001). The main risk factors associated with HCV chronic infection included male gender, being aged between 30-49 or 60-69 years old, low level of education, being unvaccinated, unemployed, not married, with personal history of blood or blood products transfusion, hemodialysis, surgical interventions, tattooing, being in contact with family members with hepatitis, with hospitalizations, imprisoned, and performing unprotected sexual contacts or with partners diagnosed with sexually transmitted infectious diseases.
Conclusions: The prevalence of HCV infection in Romania is 1.21%. Additional to providing supplemental healthcare support to vulnerable populations, the current study contributes in Romania‘s national HCV elimination objectives.

Key words: hepatitis C virus – vulnerable populations – screening – prevalence – risk factors – LIVE(RO)2 program.

Abbreviations: CI: confidence interval; HCV: hepatitis C virus; OR: odds ratio; RDT: rapid diagnostic test.

INTRODUCTION

The hepatitis C virus (HCV) infection represents an important global public health problem. According to the latest estimates, the number of people infected with HCV has decreased from 180 million (2.5-3% of the global population, before the introduction of direct antiviral therapeutic regimens) to 57 million to date (with about 2.4 million in the United States and 3 million in Europe) [1,2].

The average prevalence of HCV infection is currently less than 1% worldwide, with variations between 0.1% and 22% [3]. The seroprevalence, which is the presence of anti-HCV antibodies in general population, is low (< 2.5%) in the US and Western Europe [4], intermediate (2.5–5%) in Eastern Europe, the Mediterranean basin, and the Middle and Great East (> 5%), while in some regions of Africa (Egypt, where the average prevalence of HCV infection is 22%, with some rural communities experiencing as high as 50%), the Middle East (Iran, Pakistan), and the Asia-Pacific area (China, Indonesia) is alarmingly high [5].

Recent statistical reports showed that Romania has the greatest prevalence of HCV in Europe, most recently estimated at 2.7% meaning approximately 550.000 patients with detectable HCV viremia [6-8]. Historically, HCV prevalence in Romanian population was very high, being 5.9% in 1990, 3.23% in 2010 [9, 10]. Worldwide, the infection with HCV was one of the main causes of chronic viral hepatitis (64%), liver cirrhosis (59%), and a frequent need for liver transplantation (approximately 1/3 of the indications for liver transplantations being made for patients with chronic HCV infection) [11]. An estimate of the population's HCV infection is crucial for a nation's health policy since it enables the design of therapeutic and preventive actions as well as the assessment of whether or not infected individuals require treatment.

With some of the highest infection rates in the European Union, Romania's HCV epidemiology offers distinct patterns of prevalence and transmission and presents a serious public health concern [12]. This calls for a targeted investigation to properly guide public health initiatives.

In order to address this significant public health problem and to achieve the goal proposed by the World Health Organization (WHO) of micro-elimination of viral hepatitis C by 2030 [13], a significant effort was made in Romania by carrying out a national screening project that also aimed at patients with HCV, "Integrated regional program for prevention, early detection (screening), diagnosis and referral to treatment of patients with chronic liver diseases secondary to viral infections with hepatitis B/D and C viruses - LIVE(RO)2", financed by POCU/755/4/9/. The goal of this national priority viral hepatitis screening program was to increase patient access to high-quality healthcare. The implementation in Romania of this integrated viral hepatitis screening project aimed at improving patients' access to quality and sustainable medical services to promote social inclusion, combat poverty and any form of discrimination was a national priority being in full agreement with the provisions the national strategy regarding social inclusion and poverty reduction 2015-2020.

The goal of this program was to identify people who were infected with HCV, particularly in populations who were at risk (vulnerable populations), and to offer them preventive and necessary medical care. At the same time, the LIVE(RO)2 program tried to identify the prevalence of HCV infection and the risk factors, especially among the vulnerable population (poor people, uninsured, self-employed in agriculture, from rural areas, who do not have identity documents, from foster care, who have left the child protection system, homeless people, Roma people, people with disabilities, from single-parent families, people suffering from addiction to alcohol, drugs and other toxic substances, victims of domestic violence or victims of human trafficking) in order to help implement future public health strategies.

The objective of the study responds to a theme of national interest in the field of health, namely the highlighting of some aspects that can influence the decision-makers in the health services to approach some policies to reduce the incidence of priority communicable diseases such as hepatitis C and ensure patients' access to antiviral treatments (Objective 2.5 of the National Strategy of Health 2014-2020).

METHODS

Study Design

We performed a prospective cohort study that included 320,000 individuals screened for HCV infection recruited between July 2021 and November 2023. The screening was funded by the national project LIVE(RO)2 (co-funded by The Human Capital Operational Program, POCU/755/4/9/136208 for the Southern region and POCU/755/4/9/136209 for the Eastern region) that aimed to detect, diagnose, treat, and prevent HCV infections in vulnerable populations. Approximately 1,500 public healthcare professionals (including general practitioners, epidemiologists, infectionists, gastroenterologists, radiologists, internists, oncologists, as well as medical nurses) in 24 counties performed a three-stage screening for HCV infections in vulnerable and other socially categorized populations. All patients identified with HCV infection with the help of rapid diagnostic tests (RDT) performed in family practitioners' offices, were directed to the following tertiary centers for liver disease staging and evaluation to administer treatment with direct antivirals.

Three hundred and twenty thousand adults (>18 years old) were included in the study disregarding their age and gender, but considering their appurtenance to vulnerability groups: residents of areas with a high vulnerability prevalence, individuals experiencing poverty, uninsured individuals, self-employed individuals in agriculture, residents of rural areas, people without identity documents, individuals currently or previously in foster care, those who have exited the child social security system, homeless individuals, individuals of Roma ethnicity, individuals with disabilities-including those with complex needs-individuals who have children with disabilities, members of single-parent families, individuals suffering from addiction to alcohol, drugs, and other harmful substances, and individuals who are victims of domestic violence or human trafficking. Individuals not having permanent residency in one of the targeted 24 counties in the Northeastern, Southeastern, Southern, and Southwestern regions of Romania or being less than 18 years old were excluded from the current study. Also, pregnant women and currently imprisoned individuals, as well as individuals not agreeing an informed written consent were excluded.

All procedures were performed according to the national and European regulation regarding studies involving human patients (Declaration of Helsinki, 1975) and were approved by the Local Ethics Committee (No 8537/11.08.2020). Efforts were made to protect patient identity and personal data and all the patients agreed to a written informed consent before being included in the study. Additional permission was obtained from the patients for liver disease staging, monitoring, and blood sampling.

HCV Screening and Study Population

The screening for HCV infection in vulnerable populations was performed in a three-stage procedure (Fig. 1).

Firstly, the general practitioners collected demographic (age, gender, residency, ethnicity, education, marital status, and employment status) by performing individual interviews with the patients.

Secondly, following the interview, the general practitioner administered a rapid screening test for HCV infection (Rapid detection cassette kit anti-HCV Test, Turklab, Izmir, Turkey). Patients detected by RDT with positive anti-HCV antibodies were directed to the mentioned tertiary centers for liver

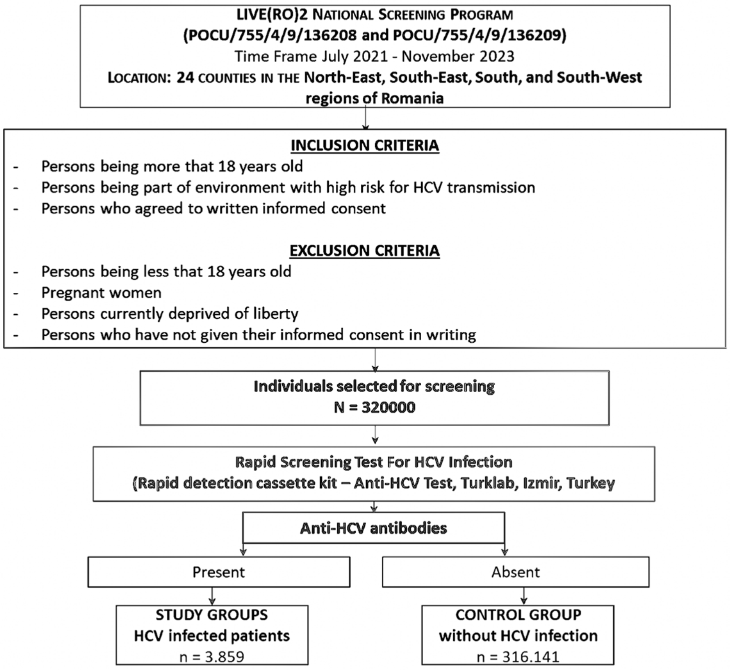

Fig. 1. Flow chart – selection of people included in screening and creation of study groups.

disease staging. Abdominal ultrasound, evaluation of liver fibrosis by transient elastography and HCV-RNA collection were performed in the hospitals. Anti-HCV antibodies positive raised the possibility of a viral C infection, which was then verified by HCV-RNA testing with a detection limit of 15 IU/mL.

Lastly, the investigators administered to each patient an epidemiological survey consisting in 20 noncolinear items that contributed to the risk factors evaluation (Table I).

The inclusion criteria for screening were: persons from 24 counties in the North-East, South-East, South, and South-West regions of Romania, persons from environments at high risk of HCV infection, aged over 18 years and who had signed the informed consent.

The exclusion criteria were: persons outside the geographical area established for screening, persons under 18 years of age, persons sentenced to deprivation of liberty, pregnant women and persons who did not sign the informed consent.

Table I. Summary of the epidemiological survey administered to the patients in the third stage of the study

ITEM	QUESTIONS
I.1.	History of antiviral vaccination (HBV)
I.2.	History of hepatitis diagnosis
I.3.	History of hepatitis treatment
I.4.	History of family contact with confirmed hepatitis virus infected individuals
I.5.	History of sexual contact with confirmed hepatitis virus infected individuals
I.6.	History of other contacts with confirmed hepatitis virus infected individuals
I.7.	History of risk professions (direct contact to possibly infected blood products)
I.8.	History of blood or blood derivates transfusions
I.9.	History of hemodialysis
I.10.	History of previous surgical interventions
I.11.	History of previous hospitalizations
I.12.	History of previous dental or oral cavity surgical interventions
I.13.	History of accidents (domestic or road crashes) requiring hospitalization
I.14.	History of accidents involving cut or puncture wounds with sharp objects or blood-contaminated objects
I.15.	History of non-prescribed injections
I.16.	History of imprisonment
I.17.	History of tattoos or piercings (including ear piercings)
I.18.	History of intravenous drugs use (unique or repeated)
I.19.	History of casual or unprotected sexual contacts
I.20.	History of sexually transmitted infections diagnosis

While assessing the risk factors associated with HCV chronic infection, the studied population was divided into two study groups based on the presence of anti-HCV antibodies in the patients' blood.

Statistical Analysis

The crude prevalence of chronic HCV infection by sex, age groups (18–29 years, 30–39 years, 40–49 years, 50–59 years, and 60–69 years), geographical regions of residence, area of residence (rural, urban), ethnic groups, educational levels, marital, social status, and for all investigated risk factors was calculated.

Univariate comparisons between categorical variables were carried out using the Chi-square test and the Wilcoxon Rank-sum test, as appropriate. The trend across ordered groups such as age groups and education level were calculated using a Wilcoxon-type test. We evaluated the association between the risk of having a chronic HCV infection and the characteristics of the participants or risk factors using an unconditional multiple logistic regression model. The dependent variable of our model was the presence or absence of markers of chronic HCV infection. The independent variables were the characteristics or risk factors to be investigated together with demographic data such as sex, age group, and area of residence (rural, urban). We tested separately the association for each investigated characteristic or risk factor. Odds Ratios (OR) adjusted for sex, age groups, and area of residence (urban, rural) were calculated with the corresponding 95% confidence intervals (95%CI). All statistical tests were two-sided and a value of p-value less than 0.05 was used to indicate statistical significance. We did not use Bonferroni correction adjustment for multiple testing. All statistical analyses were carried out using STATA/SE 11 software (Stata Corp, College Station, Texas, USA).

Ethical Considerations

The ethical principles of the declaration of 1975 Helsinki were respected, the survey was approved by the Local Ethics Committee (No. 8537/11.08.2020), and the study protocol was signed and explained in detail to all patients. Informed consent for study inclusion was obtained from all patients, thus agreeing to additional monitoring and blood sampling included in the study protocol for liver disease staging.

RESULTS

Out of the 320,000 screened individuals, 3,859 were infected with HCV meaning 1.21% prevalence (95%CI: 1.17–1.24). HCV-infected individuals were meanly aged at 65.8±12.93 years, significantly higher as compared to non-infected participants (54.03±16.41 years, $p<0.0001$) (Table II). The statistical analysis of the demographic data revealed a significantly higher prevalence among the residents of the North-Eastern region, as compared to the lowest prevalence in the South-Eastern region (1.73% versus 0.80%, at $p < 0.001$). The prevalence of HCV infection was also significantly higher in women (1.39% vs 0.89 %, $p < 0.001$) and rural residents (1.25% vs 1.1%, $p=0.0003$). No significant differences in the prevalence of HCV cases were noted depending on the ethnicity of the people participating in the screening ($p=0.8942$).

We found that in widowers (2.74%, 95%CI: 2.58–2.90) and undeclared marital status participants (2.35%; 95%CI: 1.65–3.26) the infection had a significantly higher prevalence ($p<0.001$). A significant association of marital status, education level (ISCED) with the prevalence of HCV cases was noted ($p<0.0001$) (Table II).

An association was found between being inactive (students or retirees) or unemployed with the increased prevalence of HCV infection (1.61%; 95%CI: 1.55–1.66 and 1.16%; 95%CI: 0.62-2.03, respectively, at p<0,0001).

Thus, it was highlighted that people from the Northeast-South East region of Romania have a significantly higher chance of HCV infection (OR=2.18, 95%CI: 2.04–2.32, $p<0.001$) compared to the South – South West region. Also, people from rural areas (OR=1.14, 95%CI: 1.06–1.23, $p<0.001$) and women (OR=1.58, 95%CI: 1.47–1.69, $p<0.001$) have a significantly higher chance of HCV infection (Table II).

To describe the profile of the HCV-infected patients from the specific studied population, a multivariate analysis was performed. The independent variables were included in the comparative analysis if a statistically significant influence (OR>2) on the HCV infection prevalence was obtained (Table III). In this way, the included factors were: age > 56 years, being a widower / divorced / separated and no or low education level (primary cycle education / gymnasium).

We found that people aged more than 56.5 years are the most prone to be infected with HCV.

Furthermore, the multivariate analysis of the demographic and socio-economic factors allowed the description of the profile of HCV infection increased risk population. The most important factors that contribute to the increase of HCV infection risk are: being aged more than 56 years (OR=3.469; 95%CI: 3.141–3.831, $p<0.001$) and socio-economic status of being inactive or unemployed (OR=2.714; 95%CI: 2.161–2.981, $p<0.001$). Other factors that contribute to the HCV infection risk increase are: marital status, education level, and gender (male) (Table IV).

Regarding the epidemiological survey data analysis, we found that most of the items were significantly prevalent among the HCV-infected individuals that were included in the current study (Table V). Therefore, the items regarding anti-HBV vaccination (I.1), hepatitis diagnosis (I.2), hepatitis treatment (I.3), sexual contacts with HCV-infected individuals (I.4), high contamination risk profession (I.7) provided high impact risk factors for HCV infection. Several items, such as history of other contacts with HCV-infected individuals (I.6), previous surgical interventions (I.10), previous hospitalizations (I.11), accidents (domestic or road crashes) requiring hospitalization (I.13), tattoos or piercings (I.17), intravenous drugs use (I.18), and sexually transmitted infections diagnosis (I.20), did not provide significant risk for HCV infection.

Based on the multivariate analysis of the epidemiological survey data, we could predict that individuals not being vaccinated against HBV (I.1), being previously diagnosed with hepatitis (I.2), receiving previous treatment for hepatitis (I.3), having a history of previous sexual contacts with HCV-infected individuals (I.5), having a risk profession (I.7), receiving previous blood or derivates transfusions (I.8), having previous dental or oral surgical interventions (I.12), or being previously imprisoned/ liberty-deprived (I.16) were the most prone to be infected with HCV (Table V).

Table II. Assessment of prevalence and risk of HCV infection by demographic and socio-economic factors (univariate analysis)

Number of tested persons N=320000	HCV infection / Number of tested persons	Prevalence, % (95%Confidence Intervals) (alpha = 0.05)	p	Univariate analysis Logistic Regression	
				Odd Ratio (95%CI)	p
HCV infection	3859 / 320000	1.21 (1.17 – 1.24)			
Macro-regions of development				Ref.: S – SV	
S – SV	1442 / 180000	0.80 (0.76– 0.84)	<0.0001		
NE – SE	2417 / 140000	1.73 (1.66 – 1.80)		2.18 (2.04 – 2.32)	<0.001
Environment				Ref: Urban	
Urban	983 / 89690	1.10 (1.03 – 1.17)	0.0003		
Rural	2876 / 230310	1.25 (1.20 – 1.29)		1.14 (1.06 – 1.23)	<0.001
Gender				Ref: male	
Male	1049 / 118100	0.89 (0.84 – 0.94)	<0.0001		
Female	2810 / 201900	1.39 (1.34– 1.44)		1.58 (1.47 – 1.69)	<0.001
Ethnicity				Ref: Romanian	
Romanian	3738 / 309970	1.21 (1.17 – 1.24)			
Roma	103 / 8684	1.19 (0.98 – 1.42)	0.8942	0.98 (0.81 – 1.2)	0.867
Other	18 / 1346	1.34 (0.85 – 2.01)		1.11 (0.7 – 1.77)	0.660
Age (years), mean (SD), HCV+ / HCV- Age (years), median (IQR), HCV+ / HCV-	65.8 (12.93) / 54.03 (16.41) 67 (57 – 75) / 54 (42 – 67)		<0.0001	-	-
Age group				Ref: 18-25 years	
18-25 years	15 / 16807	0.09 (0.05 – 0.14)			
26-35 years	66 / 31390	0.21 (0.17 – 0.26)		2.36 (1.35 – 4.13)	0.003
36-45 years	194 / 48546	0.40 (0.35 – 0.46)	<0.0001	4.49 (2.66 – 7.6)	<0.001
46-55 years	553 / 72575	0.76 (0.70 – 0.83)		8.6 (5.15 – 14.36)	<0.001
56-65 years	874 / 59726	1.46 (1.37 – 1.56)		16.63 (9.98 – 27.7)	<0.001
≥66 years	2157 / 90956	2.37 (2.27 – 2.47)		27.19 (16.36 – 45.2)	<0.001
Marital status				Ref: unmarried	
Unmarried	294 / 39112	0.75 (0.67 – 0.84)			
Married/Concubinage	2270 / 227449	1.00 (0.96 – 1.04)		1.33 (1.18 – 1.5)	<0.001
Widower	1064 / 38868	2.74 (2.58 – 2.90)	<0.0001	3.72 (3.26 – 4.23)	<0.001
Divorced/Separated	196 / 12732	1.54 (1.34 – 1.76)		2.06 (1.72 – 2.48)	<0.001
Undeclared	29 / 1234	2.35 (1.65 – 3.26)		3.18 (2.16 – 4.67)	<0.001
Other	6 / 605	0.99 (0.47 – 1.92)		1.32 (0.59 – 2.98)	0.500
Education (ISCED)				Ref: long-term university	
Long-term university	124 / 20491	0.61 (0.51 – 0.72)			
No education	75 / 3465	2.16 (1.73 – 2.67)		3.63 (2.72 – 4.85)	<0.001
Primary education	597 / 23923	2.50 (2.31 – 2.70)		4.2 (3.46 – 5.11)	<0.001
Gymnasium	1455 / 89915	1.62 (1.54 – 1.70)		2.7 (2.25 – 3.25)	<0.001
High school	1369 / 149042	0.92 (0.87 – 0.97)	<0.0001	1.52 (1.27 – 1.83)	<0.001
Post-secondary school	148 / 16314	0.91 (0.77 – 1.06)		1.5 (1.18 – 1.91)	<0.001
Short-term university	69 / 12519	0.55 (0.44 – 0.69)		0.91 (0.68 – 1.22)	0.533
Master's	18 / 3992	0.45 (0.29 – 0.68)		0.74 (0.45 – 1.22)	0.242
PhD	4 / 339	1.18 (0.48 – 2.56)		1.96 (0.72 – 5.34)	0.187
Social category				Ref: Employed	
Employed	615 / 117881	0.52 (0.48 – 0.56)			
Inactive (including pupils, students, retirees)	3235 / 201345	1.61 (1.55 – 1.66)	<0.0001	3.11 (2.86 – 3.39)	<0.001
Unemployed	9 / 774	1.16 (0.62 – 2.03)		2.24 (1.16 – 4.35)	0.017

HCV+: HCV-infected tested individuals; HCV-: non-infected tested individuals; OR: odds ratio; CI: confidence interval.

Table III. Cutoff values calculation for age (years) in predicting HCV infection risk

Tested independent variables	AUC	SD	p	Asymptotic 95% CI		
				Lower Bound	Upper Bound	Cutoff
Age (years)	0.769	0.004	< 0.001	0.702	0.797	56.50

AOC: area under curve; SD: standard deviation; CI: confidence interval.

Table IV. Multivariate analysis (multiple regression — logistic regression model) of the association between HCV infection and demographic and socio-economic factors

Independent variables	B	SE	Wald	p	Exp(B) OR	95% CI for EXP(B)	
						Lower	Upper
Gender (male)	0.338	0.038	80.869	< 0.001	1.402	1.303	
Age (more than 56 years)	1.244	0.051	604.160	< 0.001	3.469	3.141	3.831
Marital status (widower, divorced/separated, undeclared)	0.366	0.037	96.666	< 0.001	1.941	1.640	2.050
Education level (no education, primary education, gymnasium)	0.344	0.035	97.556	< 0.001	1.811	1.518	1.910
Socio-economic status (inactive, unemployed)	0.539	0.048	128.252	< 0.001	2.714	2.161	2.981
Constant	-7.841	0.084	8737.224	< 0.001	0.002		

For abbreviations see Table II.

DISCUSSION

Hepatitis C virus infection is currently a global public health issue of great interest due to being the leading causes of chronic liver diseases, such as cirrhosis and hepatocellular carcinoma. Despite the severe consequences of long-term infection with HCV, it is encouraging that direct-acting antivirals are providing efficient eradication of the viral infection within 8 to 12/24 weeks of treatment [13]. However, treatment approaches are only a part of a successful elimination program, while population screening seems vital.

The current study reported data on the prevalence of viral hepatitis C in several categories of population with increased vulnerability and trivial access to healthcare services. Our analysis of the recent reports regarding the prevalence of viral hepatitis C in Romania greatly motivated the current screening program to target patients with specific demographic and socioeconomic description and thus to participate to the worldwide healthcare efforts, according to the global strategy of WHO which aims at eliminating viral hepatitis by 2030. The strategy includes lowering the viral hepatitis incidence by 90%, diagnosing 90% of infected people, providing access to therapeutic programs to 80% of the eligible patients and reducing mortality due to liver failure by 65%, while the means and techniques are not restricted but adjustable to epidemiological premises of each targeted population [2].

Further national and European policies regarding the control of infectious disease spreading added substantial relevance to the scope of our endeavors that were encouraged by the European Union by cofinancing. In this way, viral hepatitis screening increased patient access to high-quality healthcare and aligned to the international strategy regarding social inclusion and poverty reduction 2015-2020 [2]. While some countries of the EU/EEA space are currently on track with the WHO targets, others that are not benefiting from political support or sufficient resources seem far from attaining the assumed threshold [14]. Tomadakis et al. [15] explained that the difference between successful elimination and delayed action is the evaluation of the national prevalence. In this context, the status of Iceland, Slovenia, and the Netherlands (with low HCV prevalences, <0.1%) were compared to Romania or Estonia (with higher prevalences, >1.5%).

By assessing the recent data on viral hepatitis C prevalence and elimination programs in other European countries, we concluded that micro-elimination is the preferred and most efficient strategy [9, 10]. Georgia and Netherlands were two of the first European countries to target the limitation of HCV and other virus transmission by micro-elimination, while Germany and Australia performed extended population screening [16, 17].

The overall prevalence of HCV infection in the Dutch population is one of the lowest worldwide, while Egypt had the most successful HCV eradication campaign, back in 2015 [18, 19]. These could be due to the ease of access to sexually transmitted infections screening and treatments [18] as well as intensive political endorsement [19].

Other good examples of substantial political endorsement in eradicating hepatitis virus are Portugal and the United States of America [20]. The advantages offered by the screening beyond high-risk population was documented by Sharma M et al. who performed a study on the prevalence of HCV infections in Qatar [21]. As most of the HCV infections are silent due to lack of symptoms until the liver is compromised, many cases remain hidden in several subpopulations (such as young asymptomatic people being indirectly at risk or unaware of being exposed) [22].

Table V. Epidemiological survey data statistical analysis

	HCV+ per TTI, n			Prevalence, %			p	Univariate analysis Logistic regression		Multivariate analysis Logistic regression		
	No	**Yes**	**Not known**	**No**	**Yes**	**Not known**		**OR (95% CI)**	p	**Ref.**	**OR (95%CI)**	p
I.1. Anti-HBV vaccination	3390 / 270814	152 / 24702	317 / 24484	1.25	0.62	1.29	< 0.0001	2.12 (1.75 – 2.57)	< 0.001	Yes	2.33 (1.96 – 2.76)	< 0.001
I.2. Hepatitis diagnosis	2489 / 312374	1271 / 4533	99 / 3093	0.80	28.04	3.20	< 0.0001	11.78 (9.55 – 14.54)	< 0.001	No	7.51 (6.49 – 7.85)	< 0.001
I.3. Hepatitis treatment	3129 / 316779	660 / 1796	70 / 1425	0.99	36.75	4.91	< 0.0001	11.25 (8.68 – 14.57)	< 0.001	No	2.05 (1.79 – 2.34)	< 0.001
I.4. Family contact with confirmed infected individuals	3034 / 277609	299 / 17380	526 / 25011	1.09	1.72	2.10	< 0.0001	1.23 (1.06 – 1.42)	0.005	No	0.7 (0.75 – 1.01)	0.071
I.5. Sexual contact with confirmed infected individuals	3217 / 287692	99 / 4239	543 / 28069	1.12	2.34	1.93	< 0.0001	5.21 (3.98 – 6.51)	< 0.001	No	1.45 (1.12 – 1.87)	0.004
I.6. Other contacts with confirmed infected individuals	2879 / 258581	83 / 5709	897 / 55710	1.11	1.45	1.61	< 0.0001	1.11 (0.88 – 1.39)	0.370	No	-	-
I.7. Risk professions (direct contact with infected blood products)	3708 / 308899	88 / 3491	63 / 7610	1.20	2.52	0.83	< 0.0001	3.1 (2.24 – 4.29)	< 0.001	No	2.57 (2.44 – 2.74)	< 0.001
I.8. Blood or derivates transfusions	3111 / 301605	631 / 14431	117 / 3964	1.03	4.37	2.95	< 0.0001	1.5 (1.23 – 1.84)	< 0.001	No	2.95 (2.67 – 3.26)	< 0.001
I.9. Hemodialysis	3803 / 318042	19 / 533	37 / 1425	1.20	3.56	2.60	< 0.0001	2.05 (1.93 – 4.83)	< 0.001	No	1.33 (0.78 – 2.25)	0.293
I.10. Previous surgical interventions	1280 / 153693	2548 / 164305	31 / 2002	0.83	1.55	1.55	< 0.0001	1.01 (0.7 – 1.43)	0.993	No	-	-
I.11. Previous hospitalizations	502 / 84406	3335 / 233752	22 / 1842	0.59	1.43	1.19	< 0.0001	1.2 (0.79 – 1.83)	0.403	No	-	-
I.12. Dental or oral cavity surgical interventions	1532 / 163682	46 / 2266	2281 / 154052	0.94	2.03	1.48	< 0.0001	1.38 (1.03 – 1.85)	0.033	No	1.33 (1.24 – 1.42)	< 0.001
I.13. Accidents (domestic or road crashes) requiring hospitalization	3642 / 308628	166 / 9250	51 / 2122	1.18	1.79	2.40	< 0.0001	1.35 (0.98 – 1.85)	0.065	No	-	-
I.14. Accidents involving cut or puncture wounds with sharp objects or blood-contaminated objects	3166 / 277581	434 / 22962	259 / 19457	1.14	1.89	1.33	< 0.0001	1.43 (1.22 – 1.67)	< 0.001	No	1.15 (1 – 1.32)	0.046
I.15. Non-prescribed injections	3649 / 304203	85 / 4757	125 / 11040	1.20	1.79	1.13	0.0008	1.59 (1.2 – 2.1)	0.001	No	0.86 (0.71 – 1.04)	0.116
I.16. Imprisonment/ liberty deprivation	3792 / 317132	35 / 1309	32 / 1559	1.20	2.67	2.05	< 0.0001	1.31 (1.12 – 2.13)	0.004	No	1.5 (1.02 – 2.2)	0.038
I.17. History of tattoos or piercings (including ear piercings)	1990 / 179153	1850 / 139709	19 / 1138	1.11	1.32	1.67	< 0.0001	1.27 (0.81 – 1.96)	0.312	No	-	-
I.18. Intravenous drugs use	3830 / 317980	8 / 475	21 / 1545	1.20	1.68	1.36	0.5427	1.24 (0.55 – 2.83)	0.603	No	-	-
I.19. Casual/ unprotected sexual contacts	3407 / 287957	326 / 25017	126 / 7026	1.18	1.30	1.79	0.00003	1.38 (1.12 – 1.7)	0.002	No	1 (0.88 – 1.13)	0.999
I.20. Sexually transmitted infections	3706 / 310997	18 / 1161	135 / 7842	1.19	1.55	1.72	0.0002	1.11 (0.67 – 1.82)	0.674	No	-	-

HCV+: HCV-infected tested individuals; TTI: total tested individuals; OR: odds ratio; CI: confidence interval.

Thus, in some high-income countries, such as Germany, the preferred approach to achieve the WHO target by 2030 seemed the addition of screening for hepatitis viruses infection within the general health examination for insured individuals over 35 years old, so more than those population categories at risk [17]. However, the reports of successful elimination from Alaska, Netherlands, Switzerland, Egypt, the Republic of Georgia, Australia, and Iceland and the precedent offered by the efficient elimination of HIV infection in specific settings give us reasons to consider that micro elimination is a good strategy in the case of HCV infections [20].

Despite the latest analyses of the European Centre for Disease Prevention and Control that reported that the goal of the international strategy of eliminating viral hepatitis is far from being achieved by 2030 in many countries [23], our screening contributed with a step forward towards the target. During the current screening program, we tested 320.000 individuals in 2 and half years (see Table II). This was the joint huge effort of more than 1500 public healthcare professionals in 24 Romanian counties. Considering the previous experiences of micro elimination in fellow European countries, we targeted vulnerability groups: residents of areas with a high vulnerability prevalence, individuals experiencing poverty, uninsured individuals, self-employed individuals in agriculture, residents of rural areas, people without identity documents, individuals currently or previously in foster care, those who have exited the child social security system, homeless individuals, individuals of Roma ethnicity, individuals with disabilities-including those with complex needs-individuals who have children with disabilities, members of single-parent families, individuals suffering from addiction to alcohol, drugs, and other harmful substances, and individuals who are victims of domestic violence or human trafficking. There are also several previous studies addressing the prevalence of HCV infection in high-risk populations, such as ethnic citizens [24] or individuals with frequent hospital admissions [25, 26]. In these studies, reports regarding the HCV infections prevalence in multicentric (large medical care campuses in Bucharest, Iasi, Cluj, and Timisoara) or small-scale (one county, Cluj) population samples could be found together with preliminary steps towards micro-elimination of HCV infection as early as 2016 [25].

We found that male gender, as well as being older than 56 years, are significant demographic factors indicating a possible HCV infection. According to the latest Annual Epidemiological Report of European Centre for Disease Prevention and Control, HCV cases were predominant in males, the male-to-female ratio being 1.6:1 in all European countries that reported data for the survey [27]. Yue et al. [28] reported that male sex and advanced age are also important HCV-associated factors in the Chinese population. Despite the general vulnerability of males to be infected to HCV, several reports also documented the predominance of female sex among the HCV-infected individuals, including a previous national survey performed on the general population of Romania [29]. Yue et al. [28] explained that these differences could occur due to the traits of the recruited individuals, as for example, the prevalence of HCV infections is higher in women by contrast to men that use intravenous drugs. Moreover, differences should also occur by function to residency area (rural versus urban), as it could be concluded by our data ($p < 0.001$, Table II). Regarding the implication of age in HCV infections prevalence, our data suggested that being aged between 30-49 or 60-69 years old is a significant risk factor (Table II). Other wider studies performed on the general population, showed that the prevalence of HCV infections with old age could be explained by the cumulative effect of exposure to HCV transmission risks over a lifetime [19, 30]. Also, another explanation is that the effects of HCV infection on the host become visible later in life, when the damage to the liver is already in a severe stage leading to immediately seeking for medical care.

The year of 2015 became a milestone in the worldwide timeline of eradicating HCV as the rate of detecting infections became equal to the rate of viral elimination by treatment [20]. However, the experience provided not only by AIDS epidemy but also by other transmissible diseases, such as malaria, tuberculosis, and COVID-19 showed that identifying HCV-infected individuals is insufficient. Treating the patients to obtain sustained virological response is a goal as important as detecting the infection. Previous studies have shown that wide screening campaigns may not be as successful as those that include both detection and treatment ("test and treat", Sisha et al. [20]). The reason of this phenomenon is that several subtypes of vulnerable population have decreased or no access to medical care (e.g. homeless people, drug consumers, or others that are often uninsured or not responding to follow-ups). Our data showed that less than 1.2% of the recruited participants were intravenous drug consumers, of which 2% were infected with HCV (see Table V). Consequently, to the previous data, our results would not suggest that intravenous drug use is not a risk for being infected with HCV, but that this vulnerable category has decreased or no access to medical care.

Another important reason of combining screening with treatment is reducing the costs of testing (by limiting re-testing of the same individual) and also the costs of treating HCV-associated cirrhotic or malignant processes. The burden of HCV transmission is often supported by the public healthcare systems which greatly depend on the committed healthcare strategies. In this way, due to increased costs, less than 30% of the detectible HCV infections are diagnosed and treated in some low- and middle-income countries [13]. Moreover, Alvis et al. [16] suggested that additional efforts to isolate and treat HCV-infected microsites are needed especially in Eastern and Central Europe. HCV treatment costs were severely affecting United States of America insurance providers and healthcare systems recently. A recent study in Qatar reported that attaining the WHO target by 2030 would require doubling current funding in this direction [31]. In contrast, countries such as France and Netherlands are fully supporting the treatment costs from the national medical insurance system [20].

The increase in liver cancers prevalence could not be attributed solely to HCV-related causes, but also to the ageing population and the delay in introducing direct-acting antivirals as treatment for HCV infections in countries with low-income [18]. By analyzing the progress of Netherlands and Switzerland in eliminating HCV especially in men having sex with men micro-population, Popping et al. [18] and Thomas et al. [20] noted that the costs of efficient healthcare programs are extremely high at the beginning and at the end of implementation, but could be successfully supported by the national healthcare providers. Also, further comparative analyses between high-income and low-income countries pointed out several differences regarding the source of HCV infection.

Despite being residents in more than half of Romanian counties, the HCV-infected patients that were identified through screening had a net average income estimated at (~ 520 €/ month) equivalent to only half of the national average net income (~ 1100 €/ month). Yet, despite the fact that the population of vulnerable categories that were not infected with HCV had a significantly higher net average income (~ 695 €/ month, $p < 0.001$) compared to HCV-infected patients, their net average incomes were still substantially lower than the national average.

Thomas et al. [20] showed that drug use and imprisonment are the most prevalent cause of HCV infection in high-income countries, whereas others are failing to report important risk factors for HCV infection, such as unsafe medical exposures. The latter was also documented as one of the main risk factors for HCV infection in low and middle-income countries [23]. Our data showed that having a risk profession (that involve direct contact or possible accidents of cutting or puncture wounds with infected blood products), as well as receiving transfusions, hemodialysis, or dental/ oral cavity surgical treatments, and imprisonment were significantly increasing the risk for HCV infection. Multivariate analysis of the data regarding these risk factors showed that receiving transfusions, having a risk profession, not receiving anti-HBV vaccination, and imprisonment, respectively, were among the top 5 risk factors.

This study provides solid scientific background for future preventive measures aimed at lowering the incidence and prevalence of HCV infection in vulnerable populations, as well as for the adaptation and design of healthcare services. The implementation of programs focused on techniques that could reduce the harming effects of HCV chronic infection is especially necessary in educating the general public and the official and informal healthcare practitioners on the health risks associated with HCV chronic infection. Additional to providing supplemental healthcare support to vulnerable populations, the current study contributes to Romania's national HCV elimination objectives.

CONCLUSIONS

The current prospective study regarding the prevalence of HCV infection in vulnerable populations showed that males, middle and old aged individuals, people that did not bbenefit from higher education, job, liberty, or family, living in the rural areas or in the Eastern part of Romania, with a personal history of blood or blood products transfusion, surgical interventions, tattooing, HCV contact in familial or sexual conditions are the most predisposed to be infected with HCV. These results are relevant in designing future preventive measures addressing the reduction of HCV chronic infections and their effects, as well as in educating people to prevent the exposure to infection risk factors, in line with the current global strategy of WHO which aims at eliminating viral hepatitis by 2030.

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Authors' contributions: A.T., C.S. C.S.P. and L.G. were involved in the study design and conceptualization. L.H. C.M. I.G., A.M.S. designed the methodology. S.I., L.H., C.M., I.G., A.M.S., S.C., T.C, S.Z., R.N., E.S., A.R., R.S., C.C, E.T., G.B. and A.S acquired the clinical data. M.M. and F.F performed the data analysis. L.H., M.M., I.M.B and A.T. interpreted the data and drafted the manuscript. C.S. and L.G. revised the manuscript for important intellectual content and were involved in the study supervision. All authors have read and agreed to the submitted version of the manuscript.

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