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The Prevalence of HCV Infection and Risk Factors in a Hospital-Based Population Screening, a First Step to the Micro-Elimination of HCV Infection in Medical Institutions from Romania - Results of the HepC ALERT Study

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ABSTRACT

Background & Aims: Elimination of hepatitis C worldwide is more feasible if micro-elimination screening strategies are adopted. We aimed to screen hepatitis C virus (HCV) in specific high-risk populations in certain sub-regions of Romania and link them to antiviral treatment.

Methods: A multicenter prospective study was conducted among the hospitalized or ambulatory adult patients from March 2019 to March 2020 in more than 20 medical institutions from 4 Romanian cities (Bucharest, Iasi, Timisoara, Cluj-Napoca). A rapid diagnostic test for HCV diagnosis was performed to all admitted patients and the positive ones were sent to gastroenterology departments for confirming the active infection, staging and treatment prescription.

Results: In total, 25,141 subjects signed the informed consent and were consequently enrolled into the study. The prevalence of anti-HCV antibodies was 1.39% (95%CI: 1.25-1.54) and increased with the number of risk factors presented by one subject. There was a positive association between the presence of anti-HCV antibodies and female gender ($p<0.001$), rural area of residence ($p<0.001$), advanced age ($p<0.001$), as well as a negative association with the education level ($p<0.001$).

Conclusions: In a hospital-based screening micro-elimination program in Romania, HCV prevalence was lower than previously reported. This is a first step towards a cost-effective screening in a well-defined group of persons at risk and provides sufficient capacity to deliver access to HCV treatment and linkage to care in Romania.

Key words: HCV – hepatitis C virus – micro-elimination – screening – link to care – public health.

Abbreviations: CI: confidence interval; DAA: direct-acting antiviral agent; HCV: hepatitis C virus; OR: odds ratio; SVR: sustained virological response.

INTRODUCTION

Chronic hepatitis C virus (HCV) infection represents nowadays a public health problem but also a socio-economic burden. The global estimated viremic HCV prevalence is around 1%, corresponding to a number of 71 million persons with positive HCV RNA worldwide. The mean prevalence in Europe is 0.65%, and Romania occupies the first place with 2.5% HCV prevalence, corresponding to 550,000 patients with positive viral loads [1, 2]. Due to the asymptomatic character of the infection, most people (>80%) are unaware of HCV positivity, are not tested, diagnosed and treated on time, in this way spreading the virus and discovering their condition when in advanced stages of liver disease [3].

An estimation of the number of people infected with HCV in the population is very important for the health policy of a given country. This allows planning of preventive and therapeutic interventions, and also determines the need for treatment of infected persons. The prevalence of anti-HCV antibodies in populations from Central and Eastern Europe varies between 0.27 and 3.5%, the number of people infected with HCV in the general population being approximately 1.16 million [4].

The ambitious goal of eliminating viral hepatitis as a public health problem by 2030 will require major efforts to increase the screening rates and consequently the diagnosing rates, as well as to link the HCV positive patients to care in Romania, similar to other countries.

With direct-acting antiviral agents (DAAs) therapy and its ≥95% cure rate, HCV elimination is clearly achievable. Increased treatment coverage and excellent sustained virological response (SVR) even in the later stages of liver disease have the greatest short-term impact on reducing morbidity and mortality, but treatment of any fibrosis stage (including F0-F1 fibrosis stage) is necessary to achieve reductions in total viremic infections and prevent ongoing transmission [5, 6]. Similar to other European countries, removing HCV treatment reimbursement restrictions in 2020 in Romania achieved great progress towards HCV elimination.

Micro-elimination, by targeting smaller and clearly delineated HCV risk groups, allows faster and better delivery of interventions. Development of possible micro-elimination scenarios breaking down national elimination goals into individual population segments enables policy makers to understand current disease landscapes on a hospital-based or regional level [7, 8]. Thus, smaller scale policy initiatives targeting specific populations or localities are a tangible step towards achieving global elimination of HCV.

We aimed to screen HCV in specific high-risk populations in certain sub-regions of Romania and link them to antiviral treatment. This integrated project of testing-diagnosis-treatment performed in over 20 medical institutions in Romania had as its objectives: micro-elimination of HCV at an institutional level among the patients that are admitted to medical units in Romania, prevention of advanced HCV liver disease, prevention of HCV transmission among the healthy population and updating the epidemiological data regarding HCV in Romania.

METHODS

A multicenter prospective study (HepC ALERT, HepC Awareness & Test-Linkage to care–Epidemiological Research-Treatment) was conducted among the hospitalized or ambulatory adult patients from March 2019 to March 2020 in more than 20 medical institutions from 4 Romanian cities (Bucharest, Iasi, Timisoara, Cluj-Napoca). Each center had included all consecutive patients addressed for routine monitoring or new patients for consultation, after signing the informed consent. A rapid diagnostic test for HCV diagnosis was performed to all admitted patients and the positive ones were sent to gastroenterology departments to confirm the active infection, staging and treatment prescription (linkage-to-care). Demographic data on age, gender, area of residence, ethnicity, marital status, education, employment, and data on risk factors for HCV infection was collected through an epidemiologic questionnaire. All data were stored while performing the test in an anonymized database that could have been accessed online at any time.

The study was approved by the Institutional Ethics Committees and conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

The prevalence of HCV positive patients was calculated with a 95% confidence interval (CI). Qualitative or quantitative variables were analyzed using nonparametric tests, the Chi-square test, Kruskal-Wallis test or the Mann Whitney U test, as appropriate. Using logistic regression, odds ratio (OR) together with the corresponding 95%CI were computed for the majority of investigated variables. All statistical tests were two-sided and a level of $p \leq 0.05$ was used to indicate statistical significance. Statistical analysis was performed using the Stata/SE 11 software.

RESULTS

Prevalence of HCV infection

In total, 25,141 subjects signed the informed consent and were consequently enrolled into the study. The prevalence of anti-HCV in the population that presented to the medical institutions in four big cities from Romania was 1.39% (95%CI: 1.25-1.54). The distribution of patients, according to the 4 cities, was as follows: Bucharest (12,875 tested persons, 1.26% HCV prevalence); Cluj-Napoca (1,281 tested persons, 2.11% HCV prevalence); Iasi (6,896 tested persons, 1.38% HCV prevalence); Timisoara (4,089 tested persons, 1.59% HCV prevalence) (p=0.054). The study population consisted of 15,802 females and 9,209 males. The HCV prevalence was similar among females and males (1.47% vs. 1.27%, p=0.199). The HCV prevalence for inhabitants of rural areas was 2.32% compared to 1.15% for subjects living in urban and metropolitan areas (p<0.001). The mean age of participants was 53.1±16.5 years. The prevalence of HCV infection increased markedly with age (p <0.001) (Fig. 1). The Roma population had the highest HCV prevalence 2.91% compared to 1.39% in Romanians or 0.57% in Hungarians (p=0.178). Subjects with university education had a significantly lower prevalence of HCV (0.54%) compared to subjects without school or just 4 years of primary school (0.54% vs. 4.07%, p<0.001). A higher HCV prevalence was observed among widowed subjects (2.73%) in comparison to married or living together as a couple (1.43%, p<0.001). The prevalence of HCV infection was also associated with employment reflecting the social status (higher percentage in retired persons or housewives, 2.29% and respectively 1.82% versus 0.65% in employees, p<0.001).

Distribution of HCV prevalence according to the medical specialty where the patient presented for evaluation was: 2.61% otolaryngology, 1.74% hematology, 1.74% orthopedics, 1.73% gastroenterology, 1.63% nephrology, 1.56% internal medicine, 1.52% general surgery, 1.01% urology, 0.78% cardiology (p=0.006).

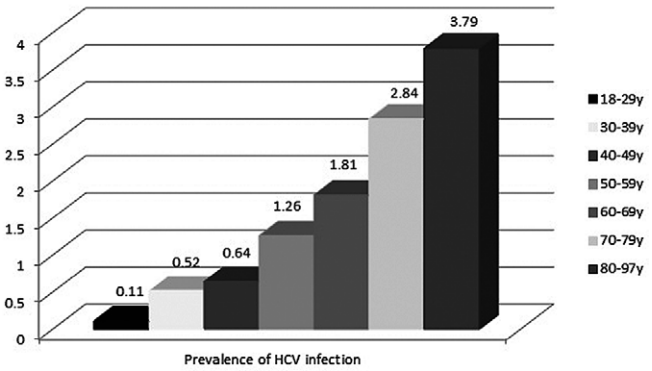

Fig. 1. Prevalence of HCV infection in different age groups.

The highest HCV prevalence (>2%) according to counties from where the patients originated were as follows: Maramures (6.62%), Tulcea (4.76%), Arad (4.62%), Dambovita (3.58%), Calarasi (2.72%), Bacau (2.71%), Vrancea (2.68%), Vaslui (2.6%), Mehedinti (2.59%), Neamt (2.42%), Botosani (2.41%), Giurgiu (2.32%), Constanta (2.22%), Suceava (2.1%).

The prevalence of HCV positive antibodies in the study cohort according to the area of development is shown in Table I.

All HCV positive persons were scheduled for further evaluation in a tertiary gastroenterology/hepatology center in their city, in order to be linked to care. The patients that presented for staging of HCV infection and were detected with a positive HCV viral load from the total tested and detected HCV antibody positive were as follows: 80.2% in Bucharest, 66.6% in Cluj-Napoca, 86% in Iasi and 81.5% in Timisoara.

Table II shows the prevalence of HCV infection according to the risk factors identified by the addressed questionnaire. Only one risk factor (sexual contacts with multiple/unknown partners) showed no association with HCV seropositivity. The prevalence of anti-HCV antibodies increased with the number of risk factors present for one subject: if a patient had ≤1 risk factors, the HCV prevalence was 0.49%; if a patient had 2-3 risk factors, the HCV prevalence was 1.33%, increasing to 2.56% in cases where a patient had 4-5 risk factors or 6.48% in cases where a patient had ≥6 risk factors ($p<0.001$). When taking into account the number of risk factors (4-17 risk factors), the regression analysis revealed a positive association between the presence of anti-HCV antibodies and female gender ($p<0.001$), rural area of residence ($p<0.001$) and advanced age ($p<0.001$), as well as a negative association with the education level ($p<0.001$). Table III depicts the OR resulted from multiple logistic regression for potential risk factors of HCV infection.

DISCUSSION

Hepatitis C is a systemic disease with hepatic and extrahepatic manifestations resulting in increased morbidity and mortality in HCV-infected patients compared to cured or uninfected individuals. Launched in 2016 by the World Health Organsation (WHO) and worldwide known, the Global Sectorial Strategy of Health for elimination of Viral Hepatitis as a threat for the health status of the population by 2030 has ambitious objectives: decrease of the incidence of the viral hepatitis by 90%, diagnosis of 90% of the infected people, access to therapy to 80% of the diagnosed and eligible persons, reduction with 65% of the liver mortality through integrated actions of awareness, testing and access to treatment [9, 10]. Also, the launch of the Elimination Manifesto on 17 February 2016 provided a starting point for action in order to make HCV and its elimination in Europe an explicit public health priority, to ensure that patients, civil society groups and other relevant stakeholders will be directly involved in developing and implementing HCV elimination strategies [11].

A key challenge to HCV elimination in Europe is the lack of reliable estimates of the burden of disease. Knowing the true burden of disease and the profile of those infected is necessary in order to design programmes and policies to scale-up prevention and treatment [12, 13].

Today, we are fighting with an important public health threat, COVID-19, which certainly needs special attention; however, we should not neglect medical care of other viruses and diseases such as HCV/HBV/HIV. Quarantine and social distancing for COVID-19 can affect diagnosis, treatment and harm reduction programs. Increasing people's awareness plays an important role in viral hepatitis elimination programs leading to more case finding [14, 15]. Thus, we consider this paper a step forward in our public health achievements for viral hepatitis elimination until 2030 in Romania, in this current difficult situation of ongoing pandemic.

Success of this ambitious goal, at least in countries such as ours, is possible only by fragmentation in various strategies/campaigns of micro-elimination (at national, institutional level, different target populations). However, this approach is used also in wealthy countries with very low prevalence such as Belgium or the Netherlands [16-18].

Table I. HCV prevalence in the screened subjects according to the area of development

N	Area of development	Tested subjects, N	HCV Prevalence	
			%	95%CI
1	North West (Bihor, Bistrița-Năsăud, Cluj, Maramureș, Satu-Mare, Sălaj)	1,124	1.96	1.29 - 2.96
2	West (Arad, Caraș-Severin, Hunedoara, Timiș)	3,887	1.44	1.11 - 1.87
3	South West Oltenia (Dolj, Gorj, Mehedinți, Olt, Vâlcea)	636	1.57	0.85 - 2.9
4	South Muntenia (Argeș, Călărași, Dâmbovița, Giurgiu, Ialomița, Prahova, Teleorman)	1,855	2.26	1.68 - 3.05
5	South Est (Brăila, Buzău, Constanța, Galați, Tulcea, Vrancea)	1,697	1.59	1.09 - 2.31
6	North Est (Bacău, Botoșani, Iași, Neamț, Suceava, Vaslui)	7,022	1.41	1.16 - 1.71
7	Center (Alba, Brașov, Covasna, Harghita, Mureș, Sibiu)	178	0.56	0.08 - 3.9
8	Bucharest - Ilfov	8,742	1.05	0.86 - 1.29
	Total screening cohort	25,141	1.39	1.25 - 1.54
Test Chi^2 (comparison of positive tests between regions)- p=0.003				

HCV: hepatitis C virus; CI: confidence interval.

Table II. Prevalence of anti-HCV antibodies by different risk factors

Risk factors (answers from the questionnaires)	Tested patients, N	HCV prevalence		p (Chi²)
		%	95%CI	
Previous known HBV/HDV				
No	24,391	1.35	1.22 - 1.51	0.007
Yes	750	2.53	1.62 - 3.94	
Known HCV (+) family members				
No	23,983	1.28	1.15 - 1.43	< 0.001
Yes	1,158	3.63	2.69 - 4.87	
Known HBV/HDV (+) family members				
No	23,911	1.35	1.21 - 1.5	0.013
Yes	1,230	2.2	1.51 - 3.18	
Deceased relatives with LC/HCC				
No	22,351	1.34	1.2 - 1.5	0.053
Yes	2,790	1.79	1.36 - 2.36	
Professional exposure to blood products				
No	20,413	1.63	1.46 - 1.81	< 0.001
Yes	4,728	0.36	0.22 - 0.58	
Blood transfusions before 1992				
No	23,915	1.08	0.96 - 1.22	< 0.001
Yes	1,226	7.34	6.01 - 8.94	
Abortion before 1990				
No	20,629	1.11	0.98 - 1.27	< 0.001
Yes	4,512	2.64	2.21 - 3.15	
Multiple surgeries				
No	19,025	1.12	0.98 - 1.28	< 0.001
Yes	6,116	2.22	1.88 - 2.62	
Multiple hospitalizations				
No	17,817	0.98	0.84 - 1.13	< 0.001
Yes	7,324	2.39	2.06 - 2.77	
Multiple stomatological interventions				
No	11,703	0.97	0.81 - 1.17	< 0.001
Yes	13,438	1.75	1.54 - 1.98	
Hemodialysis				
No	25,005	1.37	1.23 - 1.52	0.003
Yes	136	4.41	1.99 - 9.5	
Car/ Work accidents requiring prolonged hospitalization				
No	24,064	1.35	1.22 - 1.51	0.032
Yes	1,077	2.14	1.42 - 3.19	
Intravenous drugs				
No	25,085	1.36	1.22 - 1.51	< 0.001
Yes	56	16.07	8.53 - 28.23	
Sexual contacts with multiple/unknown partners				
No	23,465	1.37	1.23 - 1.52	0.306
Yes	1,676	1.67	1.16 - 2.41	
Sharing personal hygiene objects				
No	19,693	1.26	1.12 - 1.43	0.001
Yes	5,448	1.84	1.51 - 2.23	
Tatooing/piercing				
No	23,270	1.34	1.2 - 1.49	0.014
Yes	1,871	2.03	1.48 - 2.78	

HBV: hepatitis B virus; HCV: hepatitis C virus; HDV: hepatitis D virus; LC: liver cirrhosis; HCC: hepatocellular carcinoma.

Table III. Association between chronic HCV infection and a risk factor identified in the questionnaire

Risk factors	OR	95% CI	p (Z test)
Previous known HBV/HDV	0.73	0.4 - 1.33	0.306
Known HCV(+) family members	2.21	1.48 - 3.3	0.0001
Known HBV/HDV(+) family members	1.3	0.8 - 2.12	0.287
Deceased relatives with LC/HCC	0.94	0.66 - 1.34	0.729
Professional exposure to blood products	0.24	0.14 - 0.41	0.0001
Blood transfusions before 1992	3.15	2.28 - 4.36	0.0001
Abortion before 1990	1.38	1.05 - 1.8	0.020
Multiple surgeries	0.85	0.62 - 1.17	0.330
Multiple hospitalizations	1.37	1.01 - 1.87	0.045
Multiple stomatological interventions	1.14	0.88 - 1.48	0.306
Hemodialysis	0.3	0.09 - 1.05	0.060
Car/ Work accidents requiring prolonged hospitalization	0.71	0.42 - 1.21	0.204
intravenous drugs	3.7	1.19 - 11.55	0.024
Sexual contacts with multiple/unknown partners	0.92	0.57 - 1.47	0.718
Sharing personal hygiene objects	1.49	1.14 - 1.95	0.004
Tatooing/piercing	1.26	0.84 - 1.91	0.265

For abbreviations see Table II

This concept targets specific population subgroups : children (under the age of 15 years), HCV/HIV-coinfected persons, birth cohorts, haemodialysis patients, those diagnosed with haemophilia, men who have sex with men, migrants, people with advanced liver disease, people who inject drugs, prisoners, and transplant recipients [7, 15, 19, 20]. In Romania, besides the already mentioned categories, we should include as target populations: people with intrafamilial transmission of HCV, transfusions and abortions during the communist era, subjects with professional exposure to blood products and multiple hospitalizations. Also females, with advanced age, with a lower level of education and unemployed from rural areas were more susceptible to have HCV chronic infection. These results are in line with our previous research [21]. However, the overall prevalence was significantly lower (1.39% vs 3.23% then previously reported). This trend indicates a cumulative risk of HCV infection over time, suggesting at the same time a cohort phenomenon with reduced transmission in recent years due to continuous improvement in healthcare conditions. The same aspects with decreased prevalence were noted in Italy [22, 23] and Spain [24].

A Polish study [25] reported the highest ratio of positive anti-HCV results in the group of young women aged <35 years with a positive history of at least one hospitalisation (5.5%). This proportion was significantly higher compared to the group of patients with arterial hypertension (1.2%) and patients with diabetes mellitus (1.06%), also hospitalised at least once. In view of the obtained results it seems reasonable to look for new risk groups of HCV infection such as hospitalized persons in order to increase efficacy of screening and consecutively of micro-elimination.

The higher rural prevalence of HCV infection in Romania can be explained by the aging population in rural communities and a cohort effect, as well as by their hygiene conditions, lifestyle and mentalities which limit the access to medical facilities. Due to these real situations in Romania, our next screening project that will take place from 2020 to 2024 will target this kind of vulnerable population. The same results were reported in rural areas in Italy almost 20 years ago, with a HCV positivity prevalence rate of 22.4/100, with increasing age trend, with positive predominance among females; data from this study showed the effects of the inappropriate use of medical or surgery practices on the population [26].

Other identified risk factors for HCV increased prevalence are noted also in Southern Italy: abuse of intravenous drugs among people <60 years old, a history of tattooing/piercing, a history of dental surgery or surgical interventions, at least one previous blood transfusion. However, the high number of migrants from Romania to Italy can account for the rather similar risk factors in areas with high HCV prevalence.

Removing HCV treatment reimbursement restrictions in many countries was a big step forward to HCV elimination. In Romania this happened only this year, but in other countries in Europe it occurred much earlier [6, 18, 27]. Another challenge is access to DAAs therapy, especially for people from rural areas. At present, it can be prescribed and initiated only by a gastroenterologist and is available only in certain big towns. If in the future, DAAs therapy could be prescribed by other health-care professionals and would be available in local pharmacies as well, treatment access would improve and patients would be able to receive their medication more conveniently. Consistent with our findings, HCV prevalence has increased with the rising burden of risk factors as shown also in the studies from France or Canada [28-32].

Elimination of hepatitis C worldwide appears plausible, with higher chances of success if micro-elimination strategies are adopted instead of macro-elimination strategies based on mass-screening. Our study was possible by the multidisciplinary

team efforts that contributed to the testing of all admitted patients and subsequently the positive subjects were sent to treatment and care in Gastroenterology/Hepatology specialized tertiary centers. We propose this study as a possible approach to achieving HCV micro-elimination in hospitalized people. It brings up-to-date HCV prevalence data which will assist strategic micro-elimination planning that is currently lacking in Romania.

CONCLUSIONS

In this hospital-based screening micro-elimination program in Romania, HCV prevalence was lower (1.39%) than previously reported.

In a national campaign aimed at improving case finding and increasing awareness of hepatitis C, we demonstrated how targeted and locally adapted HCV testing and treating interventions may be successful in rapidly achieving micro-elimination in high risk patient populations. This is a first step towards a cost-effective screening in well-defined group of persons at risk and provides sufficient capacity to deliver access to HCV treatment and care in Romania, bringing our country closer to the achievement of the WHO objective.

Conflicts of interest: None to declare.

Authors' contributions: L.G., C.G. conceived and designed the study, and wrote the paper. S.I. performed the statistical analysis and wrote the paper. I.E.C. designed the study and performed the statistical analysis. S.I., L.H., M.C., C.C., R.N., I.G., R.S., A.M.S., C.P., D.D., R.I., R.V. tested the patients and collected the clinical data. C.P., M.D., D.D., A.T., I.S. conceived the study and revised the paper. All authors critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work.

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