RESEARCH LETTER

Towards Eradicating Hepatitis C in Spain: Early Insights From the Cantabria Cohort Study

The World Health Organization (WHO) set the ambitious goal of eliminating hepatitis C virus (HCV) as a public health threat by 2030.[1] To achieve this goal, the scale-up of direct-acting antiviral therapies (DAA) and the implementation of macroelimination and microelimination approaches are necessary cornerstones.[2,3] A Spanish population-based study between 2015 and 2017 with 12,246 participants determined an anti-HCV prevalence of 1.2% (95% confidence interval [CI] 1.0–1.4), with a prevalence of viremia of 0.3% (0.2–0.4).[4] Since then, Spain has implemented various screening strategies and simplified HCV management, which may be bringing us closer to the goal of eliminating HCV.[5] Our objective was to reassess and update the prevalence and incidence of HCV infection following the implementation of these measures, with the aim of identifying any epidemiological changes and their associated factors. Additionally, we aimed to propose new measurable markers for evaluating and monitoring HCV elimination strategies.

Here we report the initial results of a cross-sectional analysis in the Cantabria Cohort. Cantabria Cohort (clinicaltrials.gov ID: NCT05852678) is a population-based, geographically defined cohort recruiting residents of Cantabria (Spain) aged 40–69 years at baseline.[6] Cantabria covers an area of 5330 km^2 and it has a total population of 584,507 people.[7] Study participants are recruited through any of the following: 1) voluntary registration on the study website or direct telephone contact and 2) random selection (stratified by sex and age) using the Cantabrian Public Health System population database.[6] Among other major objectives, Cantabria Cohort aims to reduce HCV, HBV, and HIV infections in Cantabria by testing all participants and providing treatment for new cases.[6] Anti-HCV detection was carried out, and in positive cases, automatic viremia quantification was performed in blood samples collected at baseline (Supplementary Methods). The participants recruited by any mean between April 2021 and September 2023 were analyzed (n = 29,746, Table A1).

Anti-HCV + subjects (n = 298, 1%, 95% CI 0.9–1.1) were divided into 133 cases with spontaneous clearance and 151 cases with sustained virologic response (SVR), while 4 cases are pending definitive study. Among patients achieving SVR, 50.3% did so through an all-oral DAA regimen, while 48.3% achieved SVR with an interferon-based regimen, including either boceprevir or telaprevir. Notably, 25.2% of all cases presented with advanced fibrosis, and 11.9% were people living with HIV. Among the viremic patients (RNA-HCV+, n = 10, 0.03%, 95% CI 0.01–0.05), 7 out of ten were new cases. Nine patients started treatment with DAA. The total incidence of viremic patients of the entire population in this period was calculated (3.4/100,000 inhabitants), of which 30% were previously known, accordingly the incidence rate of new cases was 1 case/100,000 inhabitants (Figure).

Participants who have contact with HCV (anti-HCV+) were older, unmarried male and included in the study through random selection of the population compared to anti-HCV- participants (Table A2). Importantly, up to 89.9% of anti-HCV + participants aged 50–69 years (Figure F). Moreover, anti-HCV + participants came from unfavorable socioeconomic environments: they were less employed, have lower educational level and lower annual income. These results support the development of microelimination strategies targeting males born between the 1950s and 1970s from disadvantaged social backgrounds. We detected no differences regarding high alcohol intake (more than 50 g per day in women and 60 g/day in male[8]), but an increased percentage of people with advanced fibrosis (defined by fibrosis-4 index for liver fibrosis >3.25) in the anti-HCV + group. Regarding analytical data, subtle differences were observed (Table A2). Remarkably, RNA-HCV + patients showed no statistical differences with anti-HCV + but RNA-HCV- participants (Table A2). Among the common epidemiological risks associated with HCV infection and transmission, 6 viremic patients received blood transfusion, while one case suffered a nosocomial infection (Figure E). Importantly, only one of the ten cases had cirrhosis (F4) and most of the cases were detected in early stages of fibrosis (F1, n = 6).

Our study may be susceptible to selection biases due to the inclusion of volunteer participants and different recruiting methods (random vs voluntary registration), potentially limiting the conclusions in certain aspects. Noteworthy, minority populations with a high incidence of HCV infection may be underrepresented.

WHO proposed ten core indicators for assisting the monitoring and evaluation of viral hepatitis elimination plans, including prevalence, diagnosis, treatment initiation and cure of chronic HCV infection, incidence of HCV infection and deaths from hepatocellular carcinoma, cirrhosis and liver diseases attributable to HCV infection.[9] Furthermore, Polaris Observatory defined absolute targets for viral hepatitis elimination goals,[10] who established the target of HCV new chronic cases to ≤5 per 100,000 inhabitants. Here we report the results of Cantabria Cohort, whose study design allowed us to estimate the prevalence

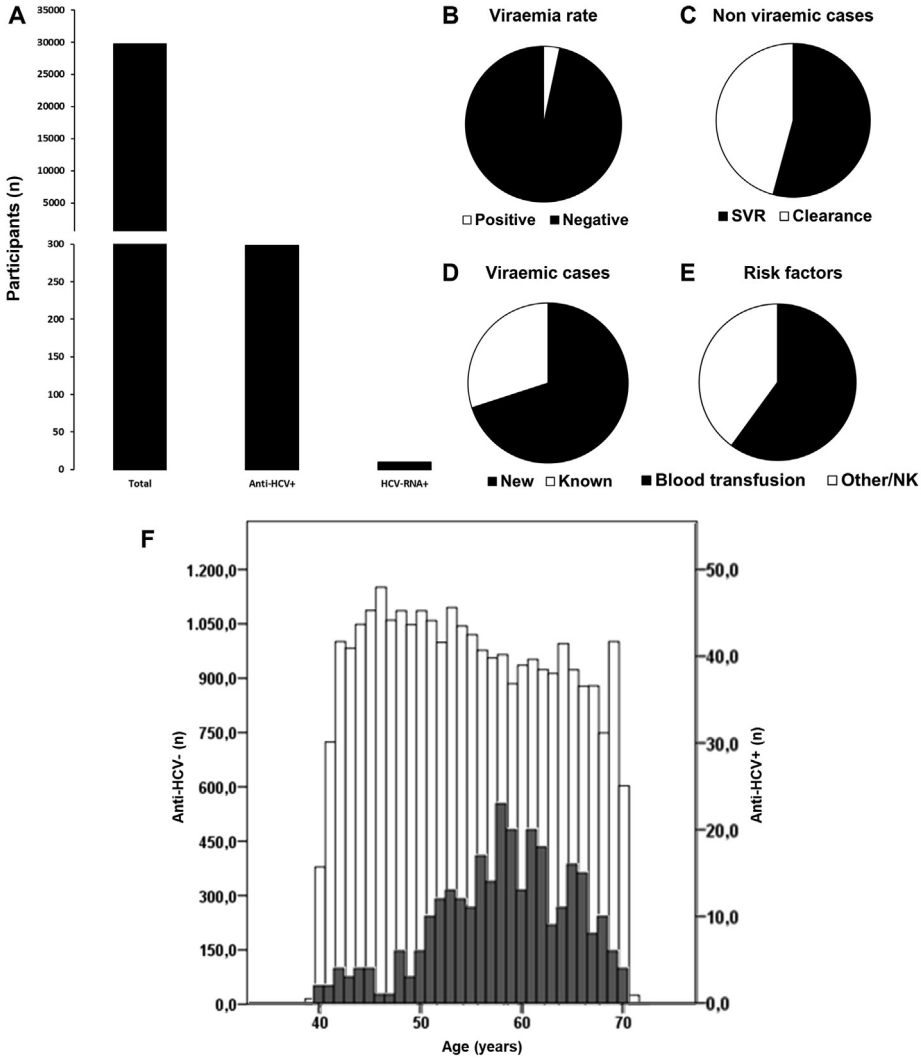

Figure. Surveillance of hepatitis C virus (HCV) in the Cantabria Cohort. (A) Number of participants in the Cantabria Cohort (total) which were positive for HCV serology (Anti-HCV+) and HCV viral load (HCV-RNA+). (B) Viremia rate, ie percentage of anti-HCV + patients who tested positive for HCV viral load. (C) Evolution of anti-HCV + patients who tested negative for HCV viral load (HCV-RNA-). (D) Percentage of HCV-RNA + patients that were newly diagnosed. (E) Main risk factors associated with HCV viremia. (F) Age distribution of anti-HCV- (white) and anti-HCV+ (grey) participants. SVR, Sustained Viral Response. Clearance: Spontaneous clearance of HCV. NK, Not known.

and incidence of HCV and demonstrate that our region has already achieved the incidence goal. As a longitudinal study, it will also provide information about cure and deaths in the long term. As a relevant aspect of this study, we consider that the reduced viremia rate (number of RNA-HCV+/total anti-HCV+, 3.36%) is a key marker of good progression in community elimination plans and an objective indicator of universal access to DAA-based therapies and cure of chronic HCV. Reduction of HCV serology may take decades to occur; however, decrease in active infection is already observable in the short term. Therefore, the viremia rate should be included as a relevant indicator for monitoring and evaluating elimination plans.

As the most outstanding fact of the study, the prevalence of viremia was less than 5% of the seropositive. This fact, associated with an incidence of 1 new case/100,000 inhabitants, places Cantabria very close to the goals set by the WHO for the definition of HCV elimination in a certain geographical region.

MARTA ALONSO-PEÑA[*]
JOAQUIN CABEZAS[*]
PAULA IRUZUBIETA
ANTONIO CUADRADO
JAVIER CRESPO
CANTABRIA COHORT COLLABORATORS
Gastroenterology and Hepatology Department, Clinical and Translational Research in Digestive Diseases, Valdecilla Research Institute (IDIVAL), Marqués de Valdecilla University Hospital, Santander, Spain

Correspondence:
Address correspondence to: Javier Crespo, MD, PhD, Gastroenterology and Hepatology Unit, Hospital Universitario Marqués de Valdecilla, Avenida de Valdecilla s/n, Santander, Cantabria 39008, Spain. e-mail: javiercrespo1991@gmail.com.

Supplementary Materials

Material associated with this article can be found in the online version at https://doi.org/10.1016/j.gastha.2024.07.013.

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***Authors share co-first authorship.**

Abbreviations used in this paper: **Anti-HCV, HCV antibodies; ALT, Alanine transaminase; AST, Aspartate transaminase; DAA, Direct-acting antiviral therapies; HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; HIV, Human Immunodeficiency Virus; ID, Identifier; PCR, Polymerase Chain Reaction; RNA-HCV+, hepatitis C viremic patients; SD, Standard deviation; SVR, Sustained Viral Response; WHO, World Health Organization**

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Conflicts of interest:
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Ethical Statement:
The study protocol (ID 2021.057) was approved by the Ethics Committee for Drug Research of Cantabria on 26 February 2021. The study respects the ethical principles of research with biological samples, the 1975 Declaration of Helsinki and Spanish Law 14/2007, of July 3, 2007, on Biomedical Research.

Data Transparency Statement:
Data and study materials will be made available to other researchers upon reasonable request.

Reporting Guidelines:
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