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ORIGINAL ARTICLE

Prevalence of hepatitis C virus infection according to the year of birth: identification of risk groups

K. Neukam[1,2] · E. Ridruejo[3,4] · P. Pérez[1,4] · R. H. Campos[1,4] · A. P. Martínez[5] · F. A. Di Lello[1,4]

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Abstract Hepatitis C virus (HCV) screening according to the year of birth is recommended is some countries based on epidemiological data. The aim of this study was to analyze anti-HCV prevalence among people born between 1905 and 2015 in Argentina. Patients attending a tertiary care hospital in Buenos Aires, Argentina, from 2001 to 2015, who had a determination of anti-HCV, were included. Of 22,079 patients analyzed, 1,152 (5.2%; 95% confidence interval [CI]: 4.9%–5.5%) patients showed positive anti-HCV and 729 (3.3%; 95% CI: 3.1%–3.5%) patients showed detectable viremia. Three risk groups were identified (HCV prevalence): low-risk group—outpatient clinics/emergencies (2.8%); intermediate-risk group—in-patients (8%); and high-risk group—dialysis/transplants (27.2%). In the low-risk group, being born in 1973 or before was identified as a cut-off value for the risk of anti-HCV acquisition (area under the receiver-operator characteristic curve: 75.1 [95% asymptotic CI: 0.732–0.770; $p < 0.001$]). Ninety-one patients born after 1973 (0.8%) showed positive anti-HCV versus 457 individuals born in 1973 or before (5.8%), $p < 0.001$. In this group, positive anti-HCV was observed in 252 females (2.1%) and 296 males (4.1%), $p < 0.001$. In a multivariate analysis adjusted for gender, alanine-aminotransferase levels and HIV coinfection, being born in 1973 or before was independently identified as a risk for positive anti-HCV (adjusted odds ratio: 14.234 [95% CI: 9.993–20.277]; $p < 0.001$). People born in 1973 or before without other risk factors should be included in screening programs to link the highest possible number of HCV-infected patients to appropriate care and treatment.

Keywords Hepatitis C virus · Prevalence · Year of birth · Patient management · Screening programs

✉ K. Neukam
karin.neukam@gmail.com

✉ F. A. Di Lello
fadilello@ffyb.uba.ar

[1] Cátedra de Virología, Universidad de Buenos Aires, Facultad de Farmacia y Bioquímica, Junín 956, 4° piso, 1113 Ciudad de Buenos Aires, Argentina

[2] Unit of Infectious Diseases, Microbiology and Preventive Medicine, Instituto de Biomedicina de Sevilla/Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Avda Manuel Siurot s/n, 41013 Seville, Spain

[3] Hepatology Section, Department of Medicine, Centro de Educación Médica e Investigaciones Clínicas Norberto Quirno "CEMIC", Buenos Aires, Argentina

[4] Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Buenos Aires, Argentina

[5] Virology Section, Centro de Educación Médica e Investigaciones Clínicas Norberto Quirno "CEMIC", Buenos Aires, Argentina

Introduction

It is estimated that hepatitis C virus (HCV) infection leads to almost 400,000 deaths every year [1]. Incidence rates of chronic HCV across the world fluctuate and are difficult to calculate. On the one hand, many infections go unnoticed because of the asymptomatic, often latent, nature of the disease before clinical presentation. On the other hand, adequate screening programs are unavailable in many settings. Of the estimated 71 million people who suffer from chronic HCV infection, as few as 20% are aware of their infection (WHO). The low level of access to diagnosis and treatment represents a major public health concern, especially in some developing countries [2–5]. According to the strategy developed by the World Health Organization (WHO), aiming to

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eliminate HCV infection, this issue clearly needs to be improved considerably [6].

To identify the highest possible number of HCV-infected individuals, HCV serology testing is recommended for people at risk for HCV acquisition [6]. Based on the prevalence of infection data from the USA, the year of birth has an impact on the probability of infection [7]. However, it is crucial to take into account geographic differences to identify risk groups for HCV infection. Although a vast amount of information is available for many Western countries, research on this topic in developing countries is insufficient and outdated in some cases. This is the case for Argentina, where the cases of HCV-induced liver disease are increasing [8], no large-scale population studies are available, and the overall HCV prevalence is estimated on the basis of poor data [9–11]. Likewise, the age distribution among the infected individuals is not well understood. Therefore, recommendations tailored for different populations may not be extrapolated to the Argentinian population. Studies to characterize the HCV-infected population with large sample sizes are warranted. Thus, the aim of this study was to determine the role of age as a risk factor for HCV acquisition within a large population of Buenos Aires, Argentina.

Materials and methods

Study population

In a retrospective cross-sectional study, patients who were tested for anti-HCV as part of a screening program at Centro de Educación Médica e Investigaciones Clínicas Norberto Quirno (CEMIC), a hospital located in the city of Buenos Aires, Argentina, between January 2001 and December 2015, were analyzed. The individuals were classified into five categories: patients attending outpatient clinics ("outpatient clinics"), those who were seen at the emergency unit ("emergencies"), those who were hospitalized ("in-patients"), patients undergoing dialysis ("dialysis"), and those who had received any organ transplant ("transplants").

Laboratory determinations

Anti-HCV testing was performed using anti-HCV enzyme immunoassay: AxSYM HCV V3.0 (Abbott, Wiesbaden, Germany) and ARCHITECT anti-HCV (Abbott). Those patients who tested positive for anti-HCV were then tested using a confirmatory recombinant immunoblot assay (RIBA HCV Strip Immunoblot Assay; Chiron, Emeryville, CA, USA) or PCR (Home-Brew) according to availability to detect current HCV infection. HIV was tested by AxSYM HIV 1/2 gO (Abbott) and ARCHITECT HIV Ag/Ab Combination (Abbott). HCV viral load was quantified using NASBA HCV QT (Biomérieux, Durham, NC, USA) and COBAS® TaqMan® HCV Test v2.0 (Roche Diagnostics Systems, Branchburg, NJ, USA). The HCV genotype was determined using LiPA 2.0 (Siemens, Tarrytown, NY, USA). All procedures were carried out according to the manufacturer's instructions.

Statistical analysis

Continuous variables were expressed as median (Q1–Q3) and categorical variables as numbers (percentages). The primary outcome variable was positive anti-HCV and detectable HCV RNA was the secondary outcome. The impact of categorical variables on the outcome variable was analyzed using the Chi-squared test or Fisher's exact test, when applicable. For continuous variables, the Mann–Whitney test was applied. The Youden Index J was calculated by means of the coordinates of receiver-operating characteristic (ROC) curves to determine the most adequate cut-off value for the date of birth to predict the primary and secondary outcome variables [12]. Subsequently, the negative predictive value (NPV) and positive predictive value (PPV), in addition to sensitivity and specificity, with the respective 95% confidence intervals (CI) were determined. Finally, a multivariate logistic regression analysis was conducted adjusting for those factors that were associated with a $p < 0.2$ in a univariate analysis. Statistical analysis was performed using the SPSS statistical software package release 23.0 (IBM, Chicago, IL, USA), STATA 9.0 (StataCorp LP, College Station, TX, USA), and Fisterra.com (Elsevier 2012; http://www.fisterra.com/mbe/investiga/pruebas_diagnosticas/pruebas_diagnosticas.asp).

Ethical aspects

The study was designed and performed according to the Declaration of Helsinki and was approved by the Ethics Committee of Centro de Educación Médica e Investigaciones Clínicas Norberto Quirno "CEMIC". All patients gave their written informed consent before being included in the study.

Results

Characteristics of the study population

A total of 22,079 patients were analyzed: 18,466 (83.6%) in outpatient clinics, 1,658 (7.5%) in dialysis, 873 (4%) in emergencies, 737 (3.3%) in in-patients, and 345 (1.6%) with transplants. Median (Q1—Q3) age was 37 (29–50) years and 8,747 (39.6%) were male. HIV determination was available in 9,252 patients; of these, 72 individuals (0.8%) tested positive. Median total bilirubin (Q1–Q3) levels were 0.42 (0.3–0.63)

mg/dL and median (Q1–Q3) ALT and AST levels were 17 (12–29) IU/mL and 19 (15–26) IU/mL respectively.

Prevalence of HCV infection

Positive anti-HCV was detected in 1,152 patients, accounting for an overall prevalence of 5.2% (95% CI: 4.9–5.5%). HCV genotype (GT) was determined in 228 patients detecting the following proportions: GT1a: 22.8%; GT1b: 41%; GT1 (undetermined subtype): 6.1%; GT2: 21%; GT3: 8.8%; and GT4: 0.4%). The prevalence of anti-HCV among the different subgroups were: 2.8% (95% CI: 2.6–3.1%) for outpatient clinics, 2.7% (95% CI: 1.8–4.1%) for emergencies, 8% (95% 6.1–10.2%) for in-patients, 27.9% (95% CI: 25.8–30.2%) for dialysis patients; and 23.8% (95% CI: 19.4–28.6%) for transplants ($p < 0.001$). Plasma HCV-RNA indicative of active HCV infection was detected in 729 patients (3.3%; 95% CI: 3.1–3.5%). Median (Q1–Q3) HCV RNA viral load was 6.1 (5.2–6.6) $\log_{10}$ IU/mL. Among the different groups, prevalence of active infection was: 1.4% (95% CI: 1.2–1.5%) for outpatient clinics, 1.6% (95% CI: 0.9–2.7%) for emergencies, 4.6% (95% 3.2–6.4%) for in-patients, 21.7% (95% CI: 19.7–23.1%) for dialysis patients and 20% (95% CI: 15.9–24.6%) for transplants ($p < 0.001$). This resulted in proportions of active infection among the anti-HCV positive patients of: 43.8% for outpatient clinics, 58.3% for emergencies, 57.6% for in-patients, 77.5% for dialysis patients, and 84.1% for transplants ($p < 0.001$).

Subsequently, patients were categorized into three risk groups according to anti-HCV prevalence:

1. Low-risk group: outpatient clinics and emergencies
2. Intermediate-risk group: in-patients
3. High-risk group: dialysis and transplants

Prevalence of anti-HCV according to year of birth for these groups is shown in Fig. 1. In the low-risk group, 252 of the women (2.1%) and 296 of the men (4.1%) showed positive anti-HCV ($p < 0.001$). The corresponding data for the intermediate-risk and high-risk groups were 27 (7.1%) vs 32 (9%), $p = 0.353$, and 237 (27.2%) vs 308 (27.2%), $p = 0.977$. Figure 2 shows transaminase levels according to risk group and HCV status.

Relationship between year of birth and HCV infection

The area under the ROC (AUROC) curve for the capacity of the year of birth to predict positive anti-HCV in the low-risk group was 0.751 (95% asymptotic CI: 0.732–0.770; $p < 0.001$; Fig. 3). Maximum J was 0.449 and accorded to "1973" as the year of birth. This cut-off value yielded a sensitivity of 83.4% (95% CI: 80–86.4%) and a specificity of 60.8% (95% CI: 60.1–61.5%). The NPV was 99.2% (95% CI: 99–99.4%) whereas the PPV was 5.84% (95% CI: 5.34%–6.39%). Ninety-one of those patients born after 1973 (0.8%) showed positive anti-HCV vs 457 (5.8%) individuals of those born in 1973 or before ($p < 0.001$). The AUROC for the prevalence of active infection in this group was 0.795 (95% CI: 0.774–0.505%; $p < 0.001$), the corresponding cut-off for the year of birth was likewise 1973 ($J = 0.512$). Active infection was observed in 27 patients born after 1973 (0.2%) versus 240 individuals (3.1%) born in 1973 or before ($p < 0.001$).

The AUROCs for the prevalence of anti-HCV and active HCV infection in the intermediate-risk group were 0.644 (95% CI: 0.579–0.709%; $p < 0.01$), and 0.643 (95% CI: 0.564–0.722%; $p = 0.005$), the corresponding cut-off values for the year of birth were 1975 ($J = 0.249$) and 1978 ($J = 0.283$). In the high-risk group, no cut-off value for the year of birth could be determined for anti-HCV prevalence or active infection (AUROC: 0.490 [95% CI: 0.468–0.518%], $p = 0.5$ and 0.476 [95% CI: 0.447–0.505%], $p = 0.125$; Fig. 3).

In a multivariate analysis adjusted for gender, alanine-aminotransferase levels, HIV status, and year of birth, a 14-fold higher risk for positive anti-HCV was detected for those born in 1973 or before in the low-risk group. Detailed results of the univariate and multivariate analyses are presented in Table 1.

Discussion

The data presented herein identify individuals born in 1973 or before without apparent any risk for HCV acquisition, in addition to hospitalized, dialysis, and transplant patients, as candidates for screening programs, as they presented a high prevalence of anti-HCV. Great differences in the prevalence of HCV were observed among the group categories studied, and anti-HCV prevalence in the low-risk group, which would resemble the general population in Argentina, appears to be somewhat higher than expected.

The year 1973 as the cut-off value for the year of birth enables identification of people at risk for HCV independently of well-known factors, such as elevated ALT levels and HIV coinfection. This is an important finding, as the NPV is very high for patients born after 1973 and anti-HCV testing may be discarded in this population if no other risk factor applies. On the other hand, all patients born in 1973 or before should be screened for anti-HCV regardless of their clinical derivation, as the prevalence detected in this study was more than 7-fold higher in this group and further augmented to 8% when only male patients were considered. It should also be noted that more than 3% showed active infection. Importantly, despite the association between ALT levels and the prevalence of anti-HCV, a considerable proportion of HCV-infected patients in the low-risk group showed transaminase levels below the

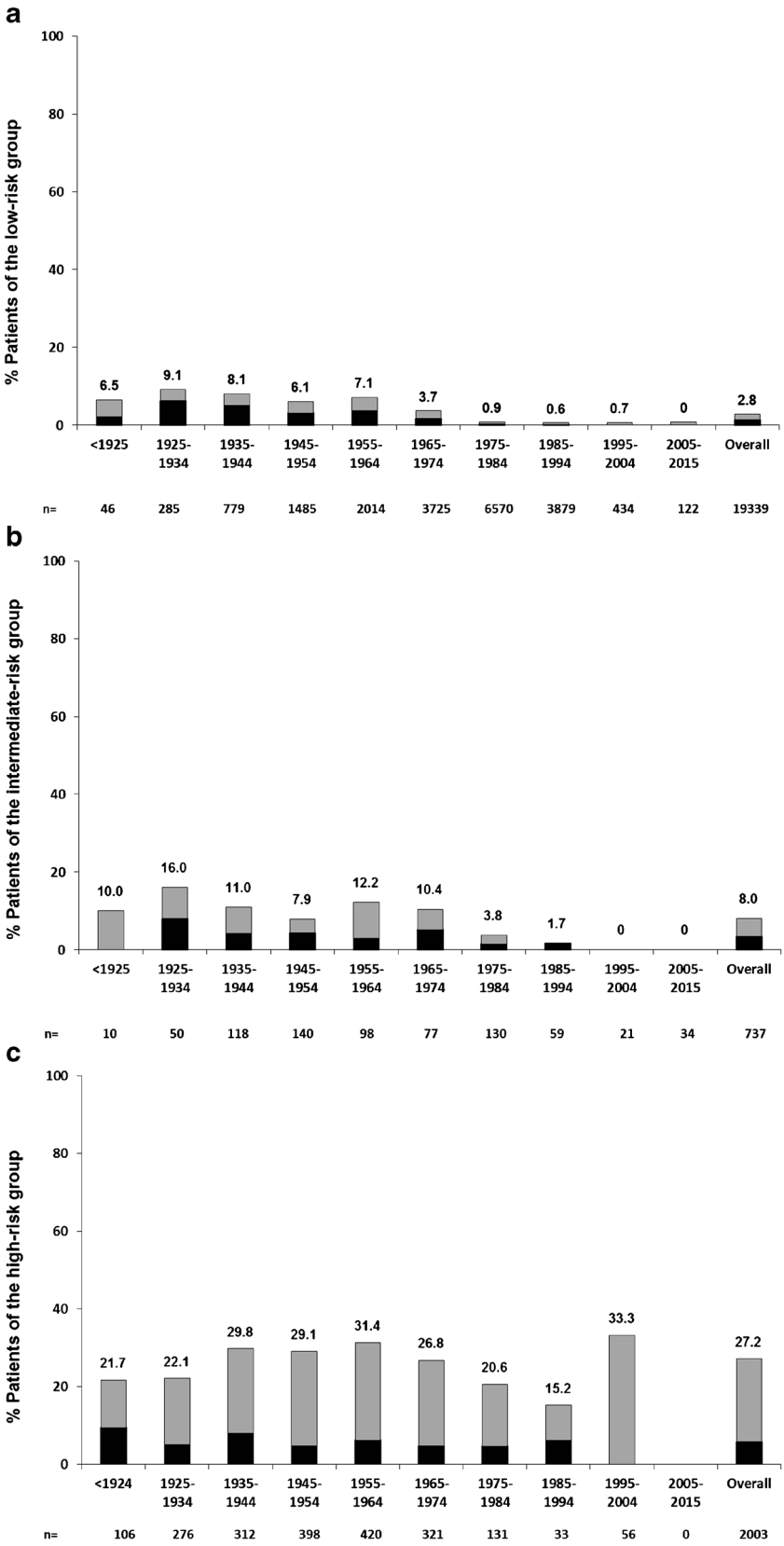

Fig. 1 Prevalence of positive anti-HCV among the different subgroups. The *black areas* indicate the proportions of individuals with active infection as determined by detectable viremia. **a** Outpatient clinics and emergencies. **b** In-patients. **c** Dialysis and transplants

upper limit of normal and most infections would have gone unnoticed if this parameter had been used as a screening criterion. These findings are in contrast to what was described for the US population, where having been born between 1945

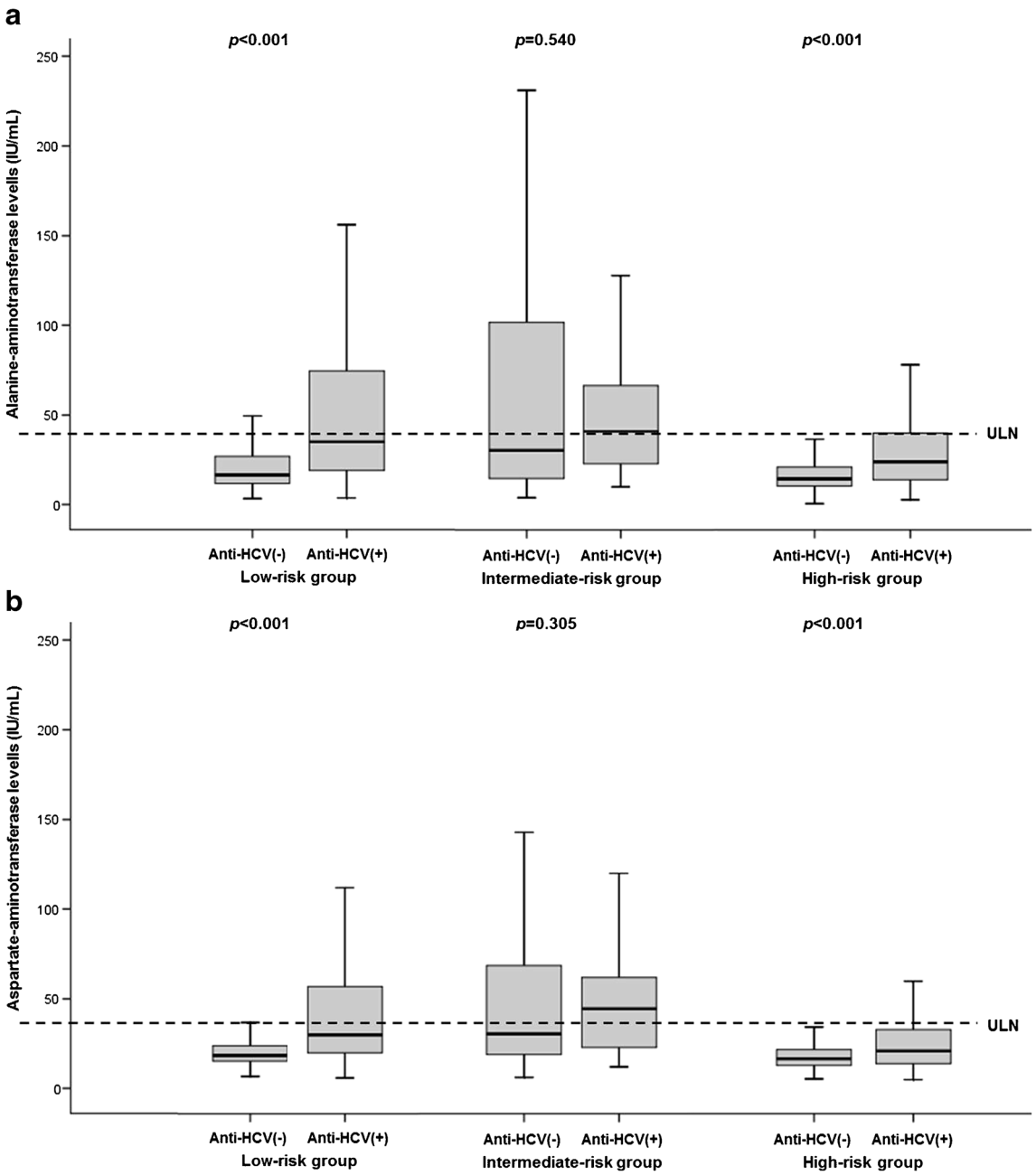

Fig. 2 Levels of **a** alanine-aminotransferase and **b** aspartate-aminotransferase at the time of HCV testing, according to HCV status for the different risk groups. *ULN* upper limit of normality

and 1965 was determined as a HCV screening criterion and included in the recommendations of the Centers of Diseases Control [13]. This birth cohort, often referred to as "baby boomers," was likewise found to represent a group with an elevated risk for HCV infection in Europe and the USA. However, this phenomenon is based on historic settings that affected Argentina far less, as it reflects the era after the end of World War II. Indeed, no evidence for increased HCV prevalence could be observed for this period in the population analyzed herein. However, the data are in accordance with those of a smaller study conducted in Argentina, where the prevalence of anti-HCV declined drastically in those individuals born after 1975 [14] and in another study that showed a similar trend [8]. Importantly, an anti-HCV prevalence of 3.7% was observed for low-risk patients born between 1965 and 1974. According to international guidelines, screening would not be a priority in this population and many infections would not be detected applying this recommendation. These findings demonstrate that individual recommendations are required for populations of different clinical derivations.

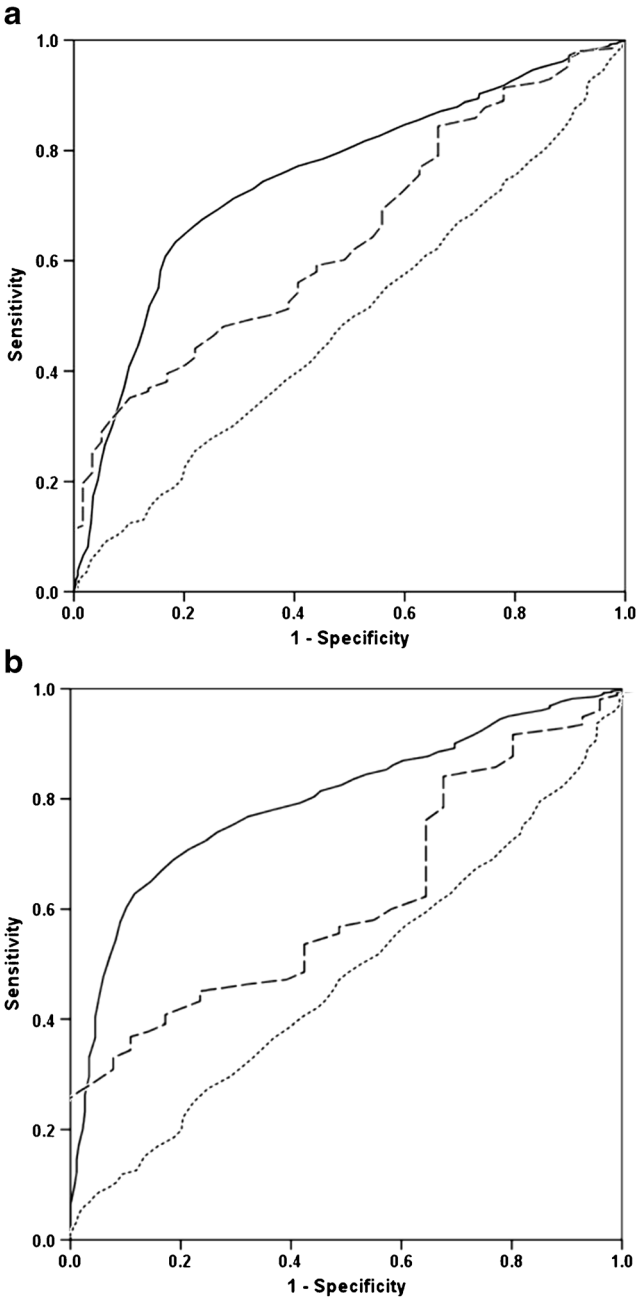

Fig. 3 Receiver-operating characteristic curves for the year of birth to predict the prevalence of **a** positive anti-HCV and **b** active infection as determined by detectable HCV RNA. *Full line*: low-risk group; *interrupted line*: intermediate-risk group; *dotted line*: high-risk group

Although a mathematically significant relationship between age and HCV infection was observed for the intermediate-risk group, which consisted of emergency patients, the prevalence of both anti-HCV and active infection was still considerably high for the favorable years of birth. This is in accordance with a recently published study conducted in an emergency department of a Northern American clinic [15]. Therefore, recommendations to waive HCV screening in this group cannot be sustained in clinical practice. No cut-off value for the year of birth could be established in the high-risk group. However, dialysis and transplant patients represent a risk group per se [16, 17], and because the very high prevalence of anti-HCV throughout all years of birth, screening for HCV should be done for all patients of this risk group.

To our knowledge, this is the largest study on the prevalence of HCV infection available for the overall population in Argentina. Importantly, the overall prevalence for all study categories was high, the lowest value still reaching almost 3% as observed in outpatient clinics. This is twice as high as that reported in a multi-objective decision analysis approach conducted by Gower and colleagues in the Argentinian adult population [9]. Likewise, studies conducted in blood donors and healthy volunteers found anti-HCV prevalence values of less than 1% [18–20]. In contrast, various spontaneous demand studies from rural areas reported seroprevalence data as high as 4.9% to 5.7% [21–24]. Furthermore, in subgroups at a high risk for HCV infection, HCV prevalence ranged from 4.3% to 54.6% [25–27]. However, on the one hand, the estimated prevalence among blood donors cannot be regarded as representing the overall population, as blood donation candidates are preselected based on a questionnaire and a physical examination. On the other hand, the opposite is true for patients at a high risk for HCV exposure such as HIV-infected people, sex workers, and injecting drug users who cannot be regarded representative for the overall population. In contrast to these studies, the design of the work presented herein provides evidence for the anti-HCV prevalence in a population that can be regarded as a good approximation to the general population, given that outpatient clinics are equally frequented by healthy subjects undergoing health revisions. Therefore, the HCV prevalence observed in this group may be extrapolated to estimate the prevalence in the overall Argentine population.

This study has limitations. First, only one single health centre in the area of greater Buenos Aires was analyzed. More rural regions where different risk factors might be present should also be taken into consideration. As mentioned above, several works have reported a high prevalence of HCV in specific rural regions [21–24]. On the other hand, a higher density or segregation of native Argentinean Amerindians may cause a lower prevalence of HCV infection, as has been described for the neighboring country, Chile [28]. Still, these would likely be isolated situations, and, furthermore, more than one third of the Argentinian population lives in the area of Buenos Aires [29]. Therefore, the study can be regarded as an acceptable approximation of the current situation. Nevertheless, studies in specific populations of Argentinian provinces are needed. Second, although the study was conducted within a screening program, physicians may have prioritized patients with apparent evidence, such as elevated transaminases, which may explain the slightly elevated prevalence observed herein. However, median transaminase

Table 1 Univariate and multivariate analysis to assess risk factors for positive anti-HCV in the low-risk group (n = 19,339)

Parameter	n	Anti-HCV (+), n (%)	p uni-variate	AOR (95% CI)	p multi-variate
Gender					
Male	7257	296 (4.1)	<0.001	1.33 (1.016–1.740)	0.038
Female	12,082	252 (2.1)		1	
Year of birth					
1973 or before	7823	457 (5.8)	<0.001	14.234 (9.993–20.277)	<0.001
After 1973	22,526	91 (0.8)		1	
ALT levels[a]					
≥ ULN	861	133 (15.4)	<0.001	6.014 (4.539–7.970)	<0.001
< ULN	5242	161 (3.1)		1	
Category					
Outpatient clinics	18,466	524 (2.8)	0.878	–	–
Emergencies	873	24 (2.7)		–	
HIV status[b]					
Positive	52	7 (13.5)	0.093	2.562 (0.869–7.554)	0.088
Negative	7726	541 (7)		1	

AOR adjusted odds ratio, *CI* confidence interval, *ULN* upper limit of normal

[a] Available in 6,103 patients

[b] Determined in 7,778 patients

levels were far below the upper limit of normal in the overall population, pointing against a bias. Furthermore, recommendations of the Argentina National Programme that promotes screening in the general population [30] were applied in the clinical practice. Finally, the result would have not been different as the age distribution would have not been affected. Prospectively designed studies are warranted to confirm these findings.

In conclusion, the data highlight the importance of screening people born in 1973 or before without other risk factors to link the highest possible number of HCV-infected patients to appropriate care and treatment. It further suggests that the prevalence of HCV infection is higher than what was previously estimated for Argentina.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

Ethical approval The study was designed and performed according to the Declaration of Helsinki and was approved by the Ethics Committee of Centro de Educación Médica e Investigaciones Clínicas Norberto Quirno "CEMIC".

Informed consent All patients gave their written informed consent before being included in the study.

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