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Major Article

Epidemiological survey of hepatitis C in a region considered to have high prevalence: the state of Minas Gerais, Brazil

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Abstract

Introduction: The prevalence of hepatitis C virus (HCV) infection is affected by demographic, virological, clinical, and lifestyle-related factors and varies in different regions in Brazil or worldwide. The present study aimed to clarify the epidemiological patterns of HCV infection in the interior region of Brazil. **Methods:** This study was conducted in the Southern Triangle Macro-region of the state of Minas Gerais, Brazil, according to the guidelines of the National Program for the Prevention and Control of Viral Hepatitis. The participants answered a structured questionnaire on social and epidemiological factors. Immunochromatographic rapid tests were used for the qualitative detection of antibodies against HCV in whole blood (Alere HCV® Code 02FK10) in adult subjects by a free-standing method. **Results:** Of 24,085 tested individuals, 184 (0.76%) were anti-HCV positive. The majority of anti-HCV-positive individuals were born between 1951 and 1980 (n=146 [79.3%]), with 68 women and 116 men. Identified risk factors included syringe and/or needle sharing ($p = 0.003$), being in prison ($p = 0.004$), and having tattoos or piercings ($p = 0.005$) and were significantly associated with the decade of birth. **Conclusions:** The study shows the importance of testing populations at risk for HCV infection, including incarcerated individuals, those with tattoos or piercings, those who share or have shared syringes or needles, and those in high-risk birth cohorts (1950s, 1960s, and 1970s) in the Southern Triangle Macro-region.

Keywords: Hepatitis C virus. Anti-HCV. Epidemiology. Prevalence. Risk groups.

INTRODUCTION

Approximately 70 million individuals worldwide are infected with hepatitis C virus (HCV)[1]. HCV causes hepatitis C, which is currently considered a global health problem by the World Health Organization. Hepatitis C is a curable but frequently underdiagnosed disease and associated with several hepatic and extrahepatic manifestations, including malignant tumors[2,3]. In 2012, the Centers for Disease Control and Prevention in the USA recommended testing all individuals born between 1945 and 1965 (baby boomers); this is because the National Health and Nutrition Examination Survey revealed that 75% of individuals infected with HCV were in this age group[4,5]. The prevalence of HCV infection is affected by several demographic, virological, clinical, and lifestyle-related factors. To establish appropriate strategies for the detection, prognosis, and treatment of this disease, it is important to understand the factors that determine the prevalence and burden of HCV infection[6].

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In Brazil, previous studies have shown that the prevalence of HCV infection increases in patients aged >40 years; almost half of patients diagnosed as HCV positive were aged 46–60 years, with the maximum prevalence among those aged 50–60 years. A population-based prevalence study performed in the capital cities of Brazil between 2005 and 2010 found that the overall prevalence of HCV infection was 1.38% (95% confidence interval [CI] , 1.12–1.6%) and 1.27% (95% CI, 1.0%–1.6%) in the capitals of Southeast Brazil[7-9].

A survey of hepatitis A, B, and C virus infection performed in 13 Macro-regions of the state of Minas Gerais in 2012 showed that the overall prevalence of HCV antibody positivity was 1.33% (95% CI, 1.09%–1.56%), with the highest prevalence (2.47%) in the Southern Triangle Macro-region[10].

The present study aimed to understand the epidemiological patterns of HCV infection in the interior region of Brazil, which until now have been evaluated mainly based on records from blood donors, volunteers, and special groups or surveys performed in restricted geographical areas or capitals[11]. Given the differences between the regions, we evaluated the prevalence of HCV infection in the Southern Triangle Macro-region of Minas Gerais. The demographic profile and related behavioral factors (lifestyle) of HCV-positive individuals in the region were analyzed.

METHODS

An exploratory quantitative cross-sectional study, with an epidemiological approach, was performed through a serological survey. The data obtained were included in the Hepatitis C Diagnosis Extension Program of the Hepatitis Outpatient Clinic of the Clinical Hospital of the Federal University of Triângulo Mineiro (HC-UFTM), in partnership with the Brazilian Society of Hepatology. The region evaluated was the Southern Triangle Macro-region, composed of 27 municipalities, with a total population of 744,497 inhabitants. The Hepatitis C Diagnosis Extension Program aimed at screening new cases of HCV infection in the Southern Triangle Macro-region (**Figure 1**).

The serological survey was performed using immuno-chromatographic rapid tests for qualitative detection of specific anti-HCV antibodies in human serum, plasma, or whole blood (Alere HCV® Code 02FK10 Standard Diagnostics, Inc., Republic of Korea). According to the manufacturer, the sensitivity of the test was 100%, and the specificity was 99.4%. The program also trained health teams on rapid test procedures.

The rapid test was performed on individuals aged ≥18 years. Individuals aged >40 years were intentionally encouraged to undergo the test. While conducting the tests, the health teams collected data on social and epidemiological factors, using a structured questionnaire (sex, age, year of birth, and risk behaviors). The risk groups (G_n) consisted of the following individuals: those born in the 1940s, 1950s, or 1960s (G_1); those who received blood and/or hemoderivative transfusion

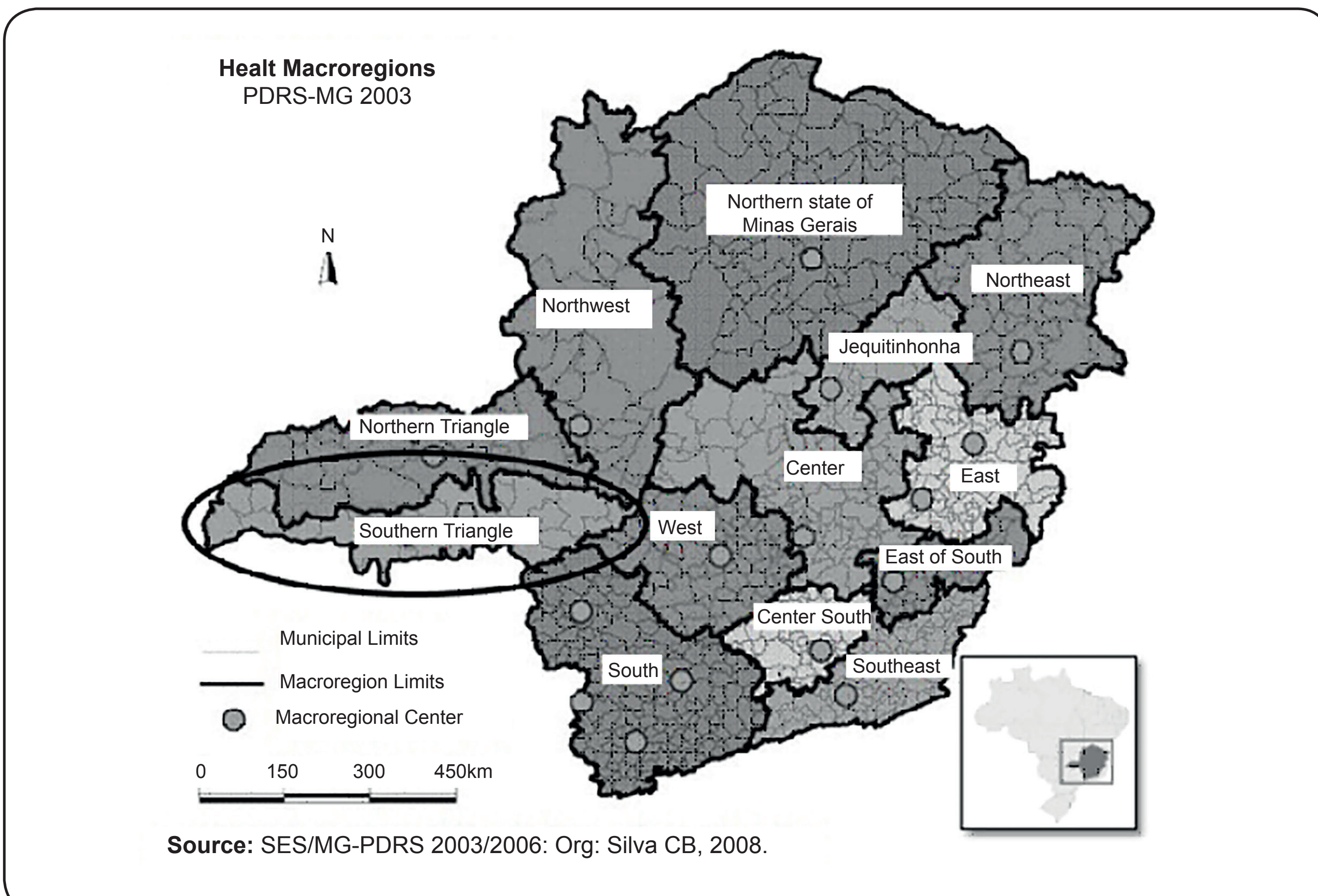


FIGURE 1: State of Minas Gerais and its Macro-regions – Brazil. In focus, the South Triangle Macro-region, object of the present study, where tests were performed by the Hepatitis C Diagnosis Extension Program of the Hepatitis Outpatient Clinic of Hospital de Clínicas – Universidade Federal do Triângulo Mineiro.

before 1993 (G_2); those sharing materials for drug (syringes, tubes, pipes) or medical drug use (glass syringes) (G_3); those with tattoos or piercings (G_4); those with occupational risk (G_5); those having unprotected sex with multiple partners (G_6); those with an HCV-carrier mother, partner, or brother (G_7); those with human immunodeficiency or hepatitis B virus infections (G_8); those in prison (G_9); and those who were homeless (G_{10}).

The tests were performed between November 2014 and March 2017. Each month, the municipality health management team sends the data to the program coordinators, in physical spreadsheets, a model previously established by these coordinators. A total of 25,909 rapid tests were performed. Tests that could not be performed (loss of kits), test doubles, and test results of individuals not residing in the region or negative test results were excluded from the analysis.

A database was created from the data returned to the program coordinator, and all statistical analyses were performed using the STATISTICA software (StatSoft, Inc., 2007). A univariate descriptive analysis was performed, using measures of central tendency and dispersion for numerical variables and frequencies (absolute and relative) for categorical variables. Then, a bivariate analysis was performed to compare the relationship of the decade of birth of the participants (31–40; 41–50; 51–60; 61–70; 71–80; 81–90) with sex (female; male) and risk (yes; no). Data were arranged in a contingency table (4×2), and the relationship was analyzed using the chi-square test (χ^2) with Yates correction. If the minimum expected value in any cell was $E < 5$, the Fischer's exact test was used. The significance level was set to $\alpha = 0.05$ in all tests.

An exploratory multivariate analysis was conducted to identify the correspondence groups between the decade of birth and remaining variables. The risk groups with higher frequency in the sample were included in this analysis, independent of the bivariate association, to ensure the explained variance. Multivariate interdependent representation was adopted using simple correspondence analysis (CA) of contingency tables followed by cluster analysis. The relationship between the variables is analyzed using a non-inferential technique, without it being necessary to designate a causal structure a priori, justifying the inclusion in this analysis of the groups with higher frequency[12].

By means of a graphic representation, the positions of the categories of each variable in the multidimensional plane can be interpreted as associations. To obtain plans that represent the configuration of the categories of the variables in space, a set of factorial axes, which are the dimensions, was calculated since the perception and representation of the multidimensional plane is feasible up to three dimensions[12].

In CA, the contribution of each variable to axis construction was measured using the absolute contribution (Cos^2); explanatory dimensions according to eigenvalues were presented. Additionally, in cluster analysis, Euclidian distance, Ward's hierarchical clustering method, and fusion level (distance) were used as measures of similarity. The results of these analyses are presented in the coordinate matrix of the explanatory dimensions and perceptual map of hierarchical clustering.

Individuals with positive results, defined as reactive to the rapid test, were admitted and followed by the Hepatitis Outpatient Clinic of the HC-UFTM. In compliance with the Declaration of Helsinki and ethical standards of Brazil, this project was approved by the Research Ethics Committee of the Federal University of Triângulo Mineiro, according to the Brazilian National Health Council resolution no. 466/2012, which deals with human research (approval no. 2.394.876).

RESULTS

Of 24,085 tested individuals, 207 were anti-HCV positive (0.86%). Excluding the nonresidents and test doubles, there were 184 anti-HCV-positive individuals (0.76%) (**Figure 2**). Of these, two individuals were aged 104 and 24 years (born in 1914 and 1994, respectively) and excluded in the multivariate analysis. The majority of anti-HCV-positive individuals were born between 1951 and 1980 (n=146 [79.3%]).

Of the 184 anti-HCV-positive individuals, there were 68 (37.0%) women and 116 (63.0%) men. The most frequent at-risk groups included individuals who were sharing syringes or needles for drug use and/or using nondisposable material for medical drug administration (23.6%); those undergoing blood and/or hemoderivative transfusion before 1993 (21.4%); those having unprotected sex with multiple partners (14.3%); and those with tattoos or piercings (9.9%). Sharing syringes and/or needles (*p=0.003*), being imprisoned (*p=0.004*), and having tattoos or piercings (*p=0.005*) were significantly associated with the decade of birth of the individuals with a positive result in the anti-HCV test (**Table 1**).

In the multivariate analysis, the explanatory perceptual map of the corresponding relationships presented a percentage of explained variance of 62.5% for five dimensions, distributed as follows: dimension 1 = 17.1% (eigenvalue = 0.284); dimension 2 = 12.6% (eigenvalue = 0.209); dimension 3 = 11.6% (eigenvalue = 0.193); dimension 4 = 10.9% (eigenvalue = 0.181); and dimension 5 = 10.3% (eigenvalue = 0.172). The analysis of coordinate distribution per factor and correlation contribution of each dimension, expressed as cosine^2 (Cos^2), are shown in **Table 2**. According to the distribution of coordinates in dimension 1, with the highest percentage of explained variance, the aspects of syringe and needle sharing, tattoos and piercing, and birth in the 1970s have similar multidimensional positioning. Moreover, the aspects of transfusions and births between 1941 and 1950 are combined (**Table 2**).

In the hierarchical analysis, according to the similarity measures, three groups of anti-HCV-positive individuals were identified based on their socioepidemiological profile: the first group consisted of individuals born between 1931 and 1940, the second group consisted of those born between 1981 and 1990, and the third group consisted of those born in the 1940s, 1950s, 1960s, and 1970s (**Figure 3**). It is noted that each level of similarity in this hierarchical analysis was obtained by a certain number of groupings. In the present study, the criterion for defining the number of groups considered as the cutoff level is the largest link distance between points, being between points 4 and 7 of the link distance. Such a cutoff level constitutes three major groups of similarity, which are defined according to the aforementioned decades.

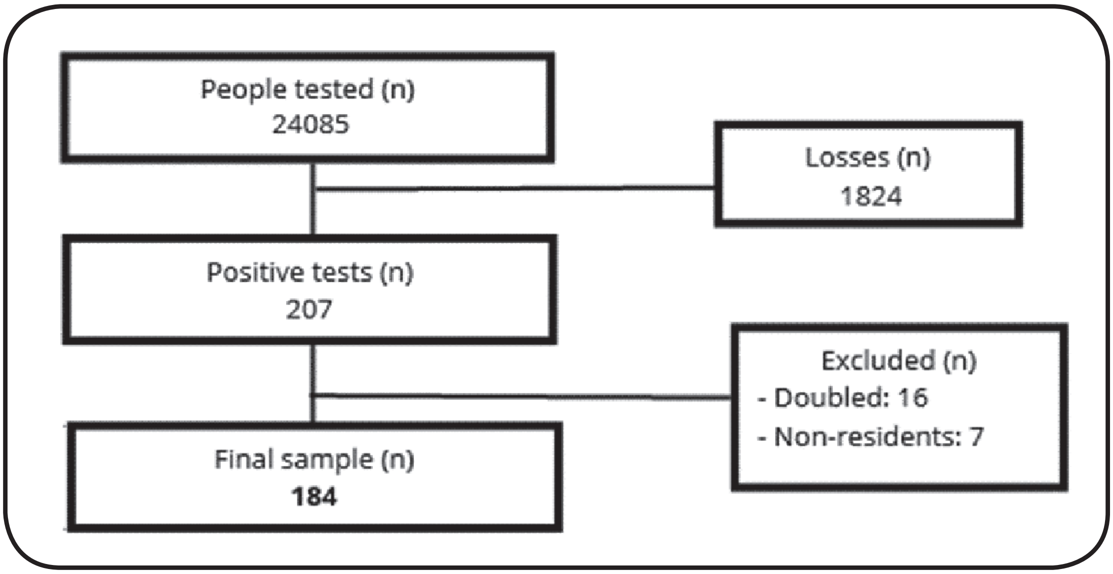


FIGURE 2: Flowchart of the tested population and final sample. Southern Triangle Macro-region, Minas Gerais, 2019.

TABLE 1: Association of socioepidemiological characteristics with the decade of birth of individuals with a positive anti-HCV test. Southern Triangle Macro-region, Minas Gerais, 2019.

Factors	**Decade**						***P*-value**
	31–40	**41–50**	**51–60**	**61–70**	**71–80**	**81–90**	
Sex, n (%)							
Female	3 (50)	11 (50)	19 (31.1)	19 (38.8)	8 (29.6)	6 (75)	0.106*
Male	3 (50)	11 (50)	42 (68.9)	39 (67.2)	19 (70.4)	2 (25)	
Risk groups‡, n (%)							
Transfusion	3 (50)	8 (36.4)	15 (24.6)	8 (13.8)	4 (14.8)	1 (12.5)	0.096*
Sharing	3 (50)	0 (0)	15 (24.6)	11 (19)	11 (40.7)	3 (37.5)	**0.003**
Tattoos or piercing	0 (0)	0 (0)	2 (3.3)	7 (12.1)	8 (29.6)	1 (12.5)	**0.005**
Occupational risk	0 (0)	1 (4.5)	3 (4.9)	3 (5.2)	1 (3.7)	0 (0)	1,000*
Multiple partners	1 (16.7)	2 (9.1)	12 (19.7)	7 (12.1)	3 (11.1)	1 (12.5)	0.811*
Carrier relatives	0 (0)	1 (4.5)	1 (1.6)	2 (3.4)	3 (11.1)	1 (12.5)	0.225
HIV/HBV positive	0 (0)	0 (0)	1 (1.6)	3 (5.2)	4 (14.8)	0 (0)	0.152
Imprisoned	0 (0)	0 (0)	1 (1.6)	1 (1.7)	6 (22.2)	0 (0)	**0.004**
Homeless	0 (0)	0 (0)	1 (1.6)	1 (1.7)	0 (0)	1 (12.5)	0.303*

*Chi-quare test (χ^2). ‡A single individual may have more than one risk factor. There are anti-HCV-positive individuals who did not present risk factors. The relative frequencies (%) presented were calculated within each decade by risk group.

TABLE 2: Coordinate matrix of the explanatory dimensions of the multivariate correspondence analysis perceptual map and explanatory contribution (Cos^2) of each dimension. Southern Triangle Macro-region, Minas Gerais, 2019.

Factors	(Coordinates per dimension)‡					(Cos^2 per dimension)				
	1	2	3	4	5	1	2	3	4	5
Sex										
Female	-0.680	-0.736	-0.190	-0.371	0.075	0.263	**0.308**	0.021	0.078	0.003
Male	0.387	0.419	0.108	0.211	-0.043					
Risk group										
Transfusion (G_2)										
No	0.268	0.222	-0.029	-0.199	-0.051	0.264	0.180	0.003	0.145	0.01
Yes	**-0.984**	-0.813	0.108	0.729	0.187					
Sharing (G_3)										
No	-0.374	0.139	-0.144	-0.032	0.119	**0.452**	0.062	0.067	0.003	0.046
Yes	**1.208**	-0.449	0.466	0.104	-0.386					
Tattoos or piercing (G_4)										
No	-0.188	0.133	0.100	-0.020	-0.086	**0.321**	0.16	0.091	0.004	0.067
Yes	**1.710**	**-1.208**	**-0.911**	0.184	0.781					
Multiple partners (G_6)										
No	-0.032	0.115	-0.196	0.131	-0.194	0.006	0.08	0.23	0.102	0.225
Yes	0.192	-0.692	**1.176**	-0.784	1.162					
Decade										
31–40	-0.381	**-1.944**	**1.821**	**2.075**	**-3.443**	0.005	0.129	0.113	0.147	**0.404**
41–50	**-1.283**	0.002	-0.848	0.623	0.499	0.226	0	0.099	0.053	0.034
51–60	-0.118	0.258	**1.037**	-0.027	0.414	0.007	0.034	**0.542**	0	0.087
61–70	0.135	0.531	-0.505	-0.372	-0.332	0.009	0.132	0.119	0.065	0.052
71–80	**1.121**	-0.763	-0.799	0.809	0.607	0.219	0.101	0.111	0.114	0.064
81–90	-0.051	**-1.792**	-0.587	**-3.103**	-1.588	0	0.148	0.016	**0.443**	0.116

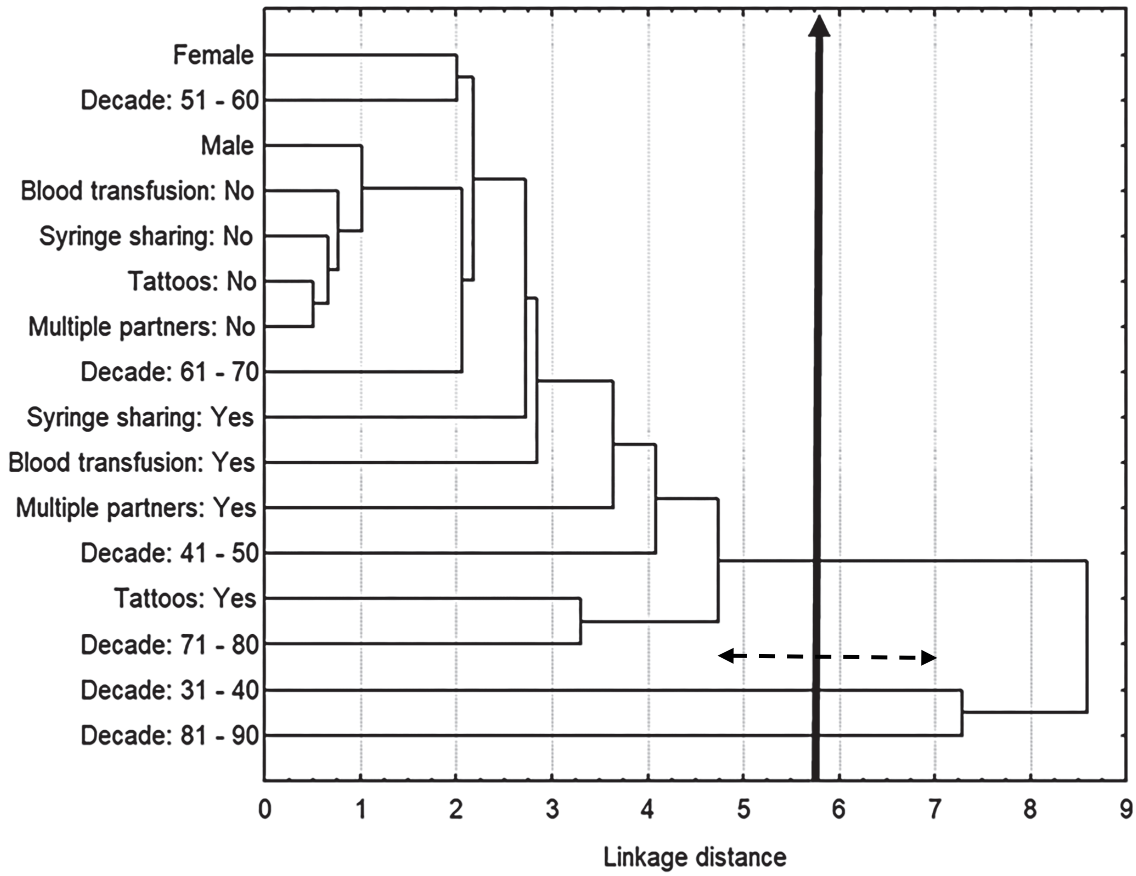
‡Coordinates of the variables in the multidimensional plane (five dimensions), according to the contribution of each variable by dimensional axis.

DISCUSSION

In the current study, among 24,085 individuals, 0.76% were found to be anti-HCV positive. This is contrary to previously published data, extracted from serological surveys performed in Brazil and the state of Minas Gerais (1.27% for Minas Gerais and 2.47% for the Southern Triangle Macro-region) [9,10].

Regarding age groups, 79.3% of the anti-HCV-positive individuals were born in the 1950s, 1960s, and 1970s. This is in agreement with the result of a study conducted in Switzerland (73.9%)[13]. In the USA, the baby boomers (born between 1945 and 1965) were found to be the main population at risk (75%)[14]. Furthermore, a 2018 study in Mongolia showed similar rates where 77% of the positive individuals were aged >50 years[15]. In contrast, in the Czech Republic, the prevalence of anti-HCV-positive cases was 1.6%, and the lowest prevalence was observed in individuals aged ≥60 years (0.2%; n=2)[16]. These differences can be explained by the exposure of the different populations to various risks factors.

In contrast to the results of the present study, in Switzerland, most HCV-positive cases were identified among individuals born before 1950, who were infected from iatrogenic contamination, including transfusion, dialysis, work accidents, injections, surgery, or dental treatments. Use of injectable drugs was the main source of exposure for individuals born between 1950 and 1979 (74.4%) and 1980 or later (67.6%)[13]. In Spain, individuals belonging to the high-risk group were born between 1955 and 1975; HCV was transmitted by blood transfusion and drug use in 46.7% and 26.7% of cases, respectively. These differences may be explained by historical and social circumstances, including



(→) Cutoff level for group definition
(←- - - - - - →) Criterion for defining the number of groups considered as the cutoff level is the largest link distance between points, being between points 4 and 7. Such a cutoff level constitutes three major groups of similarity.

FIGURE 3: Perceptual map of hierarchical clustering of social and epidemiological variables of individuals with a positive result in the anti-HCV test. Southern Triangle Macro-region, Minas Gerais, 2019.

the great epidemic of intravenous drug use in the 1980s in Spain, as well as in Brazil several years later, which was later than that in the USA and other European countries[17]. In the USA, there is a new boom; a majority of patients who were infected after 2009 reported injection drug use (IDU) (40.6%) as their source of infection, which coincides with the recent heroin use epidemic[18]. This has not yet reached the state of Minas Gerais, where crack cocaine is the most widely consumed drug. Similar to China, where amphetamine injections were a major source of infection in those aged >40 years, in Brazil, sharing of needles and syringes for these drugs also occurred. In countries where IDU is the main source of HCV infection, such as Iceland, Iran, Slovenia, Finland, Ireland, Luxemburg, Norway, Poland, Russia, and Slovakia, prevalence is higher in men born in the 1980s, whereas in countries where the infection is historically related to blood transfusion or nosocomial transmission, such as Japan, Pakistan, and South Korea, prevalence is higher in individuals born before 1965[19-21].

In the present study, we found that, of anti-HCV-positive individuals with tattoos and piercings, 29.6% were born in the 1970s. In a study in the Czech Republic, of 525 individuals with tattoos and piercings, 3.8% were HCV positive; however, the age group was not disclosed, and no evidence of a relationship between this factor and infection was found[16]. A study on 2637 individuals in Valencia, Spain, found that antibody detection was positive in 30 individuals (1.1%). The study showed that among the anti-HCV-positive cases, 23.3% had tattoos and piercing as a risk factor, as in the present study, although there is no representation regarding the decade of birth[17]. A survey of 2,128 individuals in Suriname found an association between HCV positivity and male sex, advanced age, Javanese ethnicity, and presence of tattoos[22]. In a study in Rio de Janeiro, Brazil, with 4,897 individuals tested for the presence of HCV, there were 1,180 HCV RNA-positive cases, and a significant association between RNA positivity and drug use but not with tattoos and piercings was found[23]. In the state of Goiás, Central Brazil, a study on 481 homeless men showed a significant association between HCV infection and drug use, number of sexual partners, and sexually transmissible diseases; however, there was no association between HCV infection and the presence of tattoos and piercings[24]. A study of drug users in the Island of Marajó, Amazon showed that age (35 years), presence of tattoos, IDU, sharing injection equipment, and daily and prolonged use (>3 years) of illegal drugs were associated with HCV positivity[25].

In incarcerated individuals, there was a significant association between HCV infection and being born in the 1970s, with 75% of positive individuals being born in that decade. This was also a time when sharing of syringes for drug use and having tattoos and piercings were common. A study performed in 10 prisons in the State of Guanajuato, Mexico, with 2,519 participants, showed a 4.9% prevalence of HCV infection; the prevalence increased with the number of prior incarcerations and number of tattoos before incarceration. Additionally, the highest prevalence of HCV infection was observed among individuals who injected drugs before (40%; 95% CI 25.9–54.6) and during the current incarceration (45%; 95% CI, 9.2–81.7%)[26]. In Brazil, a systematic review published in 2015 showed that the average prevalence of HCV was 13.6% among Brazilian prisoners, varying between 1.0% and 41.0% and being the lowest in the state of Espírito Santo and highest in São Paulo. However, a meta-analysis of the risk factors associated with the prevalence of HCV in Brazilian prisons could not be performed because most studies did not analyze the risk factors[27].

Effective and well-tolerated direct-acting antiviral agents are presently available for the treatment of HCV infection. However, there are a high number of undiagnosed cases, and therapeutic strategies are required to address this situation[28]. Screening based only on risk factors may result in detection of <20% of cases. HCV reporting (e.g., Australia) may improve diagnosis (proportion of diagnosed HCV infection is 75%) and benefit patients. In Australia, correct reporting of HCV infection resulted in the identification of 75% of the carriers and increased their access to care, therapy, and healing[29]. Researchers worldwide are attempting to increase the cost-effectiveness of diagnosis and prevention of HCV infection and eradication of the virus. In Australia, it became evident that testing focused on high-risk groups, such as injection drug users, prisoners, and men who have sex with other men and those in the high-risk birth cohorts, has a good cost-benefit relationship[29]. In Naples, a study on 1,315 individuals showed that individuals aged >60 years with a low purchasing power should be prioritized, considering that differences in socioeconomic conditions play an important role in transmitting this infection[30]. In Switzerland, research is focused on three groups—individuals born before 1950, especially older women (iatrogenic transmission); men born from the 1980s until the end of the 2000s (associated to IDU); and homosexual men[13].

A limitation of population-based exploratory studies is the inability to determine the time sequence of cause and effect. These studies are easy to perform and serve to formulate hypotheses on groups of interest; however, they do not represent the total population. Therefore, epidemiological conclusions from population-based exploratory studies may be limited to exposure sources for a specific population, even though the risk factors for HCV infection are well known. Finally, in the present study, individuals aged >40 years were encouraged to undergo the test, resulting in a higher proportion of baby boomers in our study. The sources of infection in these individuals may be different from those affecting younger individuals. Therefore, the analysis of the present study could have been affected by the high prevalence of anti-HCV-positive baby boomers.

The present study shows the importance of testing at-risk populations for HCV infection such as prisoners, individuals with tattoos and piercings, those who share or have shared injection or drug use equipment, and those in high-risk birth cohorts (1950s, 1960s, and 1970s) in the Southern Triangle Macro-region. Because the study was an initiative from a tertiary care teaching hospital, it allows the hospital to reach beyond its premises and provide integral training of healthcare professionals. Furthermore, this study may serve as a basis for the future development of predictive models and other correlational analyses between social and epidemiological factors of HCV carriers.

The fact that this population had not been previously studied regarding HCV infection made it possible for the present study to conduct an epidemiological survey to help public policies for health in the region. It is important to note the ease with which the rapid test was conducted in the region and used by basic healthcare teams. The assistance to patients with HCV identified by the program and strengthening of the relationship between HC-UFTM and the Municipal Health Services, who worked to track the patients so that they remained in the program and completed the treatment, should be highlighted.

The multivariate analysis revealed a scattered distribution of social and epidemiological data among HCV carriers, showing that, although hepatitis C is a single disease, it constitutes a complex mosaic for the healthcare network, regarding both its manifestations and the determinant factors of its occurrence, considering cultural, social, and economic differences between several regions where it occurs.

Therefore, the present study shows that the prevalence of anti-HCV in the Southern Triangle Macro-region population is similar to that described for Brazil by the Ministry of Health. Moreover, the study demonstrates the importance of testing populations at risk for HCV infection, including incarcerated individuals, those with tattoos or piercings, those who share or have shared syringes or needles, and those in high-risk birth cohorts (1950s, 1960s, and 1970s), in this region of the state of Minas Gerais.

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Conflict of interest

The authors declare that there is no conflict of interest.

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