

Mortality due to hepatocellular carcinoma associated with hepatitis B and C viruses in the state of São Paulo, Brazil

Mortalidade por carcinoma hepatocelular associado às hepatites virais B e C no estado de São Paulo, Brasil

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ABSTRACT: *Objective:* This study aimed to describe and analyze the temporal and spatial distribution of deaths due to hepatocellular carcinoma (HCC) associated with hepatitis B (HBV) and C viruses (HCV) in the state of São Paulo. *Methods:* This is an ecological study of HCC deaths associated with HBV and HCV in the state of São Paulo, from 2009 to 2017, with data from the Mortality Information System (SIM). The temporal trend was analyzed by linear regression with Prais–Winsten estimation. Deaths were described according to sociodemographic characteristics by means of absolute and relative frequencies and were spatially distributed according to the regional health department. *Results:* It is found that 26.3% of deaths due to HCC were associated with HBV or HCV. A higher proportion of deaths due to HCC associated with HCV was observed (22.2%) when compared to HBV (3.9%). The mortality rate due to HCC associated with HBV showed a downward trend, and the mortality rate due to HCC associated with HCV showed a steady trend. Deaths of males, white individuals, those who aged from 50 to 59 years, and those who had 8–11 years of schooling predominated. Spatial analysis revealed a heterogeneous distribution of deaths in the state of São Paulo. *Conclusions:* The downward trend in mortality rates due to HCC associated with HBV shows an important advance in the disease control. However, the mortality rate due to HCC associated with HCV has remained stable throughout the study period. The spatial distribution of deaths may contribute to raise hypotheses for deeper knowledge of these diseases in the regions.

Keywords: Mortality. Carcinoma hepatocelular. Hepatitis B. Hepatitis C. Spatial analysis. Time series studies.

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RESUMO: *Objetivos:* Este estudo tem como objetivo descrever e analisar a distribuição temporal e espacial dos óbitos por carcinoma hepatocelular associados às hepatites virais B e C no estado de São Paulo. *Métodos:* Estudo ecológico dos óbitos por carcinoma hepatocelular associados a hepatites virais B e hepatites virais C no estado de São Paulo, de 2009 a 2017, com dados do Sistema de Informação sobre Mortalidade. A tendência temporal foi analisada por regressão linear, com método de Prais-Winsten. Os óbitos foram descritos segundo as características sociodemográficas, por meio de frequências absolutas e relativas, e foram espacialmente distribuídos segundo departamento regional de saúde. *Resultados:* Dos óbitos por carcinoma hepatocelular, 26,3% foram associados a hepatites virais B ou hepatites virais C. Observou-se maior proporção de óbitos por carcinoma hepatocelular associado a hepatites virais C (22,2%) quando comparada àquela associada a hepatites virais B (3,9%). A taxa de mortalidade por carcinoma hepatocelular associado a hepatites virais B apresentou tendência de queda, no entanto a taxa de mortalidade por carcinoma hepatocelular associado a hepatites virais C apresentou tendência estacionária. Predominaram óbitos de pacientes do sexo masculino, de cor branca, de 50–59 anos e com oito a 11 anos de estudo. A análise espacial revelou distribuição heterogênea dos óbitos no estado de São Paulo. *Conclusão:* A tendência de queda nas taxas de mortalidade por carcinoma hepatocelular associado a hepatites virais B revela um importante avanço no controle do agravo. Entretanto, a taxa de mortalidade por carcinoma hepatocelular associado a hepatites virais C vem-se mantendo estável ao longo do período estudado. A distribuição espacial dos óbitos pode contribuir para levantar hipóteses com vistas ao conhecimento mais aprofundado desses agravos nas regiões.

Palavras-chave: Mortalidade. Carcinoma hepatocelular. Hepatite B. Hepatite C. Análise espacial. Série temporal.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer, the third leading cause of death of neoplastic etiology, and one of the most lethal types of cancer in the world¹. It is a malignant tumor that usually appears in cirrhotic patients and is most commonly associated with hepatitis B, hepatitis C, and chronic alcoholism². More recently, obesity has been recognized as an important risk factor for different types of cancer, including liver cancer³.

Globally, viral hepatitis accounted for approximately 1.34 million deaths in 2015. According to World Health Organization (WHO) data (2017), among deaths from viral hepatitis in 2015, 96% occurred due to complications of chronic infection, and the majority was caused by hepatitis B virus (HBV) (66%) and hepatitis C virus (HCV) (30%). Among the complications of chronic infection, 720,000 deaths from liver cirrhosis and 470,000 deaths from HCC can be highlighted⁴.

The possible underreporting of deaths due do HCC associated with viral hepatitis in Brazil and around the world is highlighted. The results of a cohort study carried out on patients with chronic HCV infection in the United States in the period 2006–2010 showed that less than one-fifth of the deaths of HCV-infected people are reported on the death certificate, which indicates a significant underestimation of the number of deaths due to HCV. Among the deaths from liver cancer, HCV was mentioned in 31% of deaths⁵.

According to the study by Tauil et al. who analyzed mortality from HBV in Brazil, from 2000 to 2009, the highest proportion of deaths due to HCC with hepatitis B as an associated cause occurred in 2001 with 6.4% (37/582)⁶. In contrast, an investigation in 19 medical centers in 8 states in Brazil identified that 39% of the cases of HCC had hepatitis B⁷. Therefore, it is very likely that there is underreporting of deaths from this disease in the country⁶.

In view of the considerations presented, this study aimed to describe deaths due to HCC associated with HBV and HCV and to analyze the spatial and temporal distribution of these deaths in the state of São Paulo, from 2009 to 2017.

METHODS

This is an ecological study, with spatial and temporal analysis of deaths due to HCC associated with HBV and HCV in the state of São Paulo, from 2009 to 2017. The study area corresponds to the state of São Paulo, which counts with 645 municipalities, spread over a territorial area of 248,219,63 km², with a total of 43,359,005 inhabitants in 2016⁸.

Data on deaths of residents in the state of São Paulo were obtained from the Mortality Information System (SIM), and data on the population living in the state of São Paulo and in the municipalities were the annual population estimates of the State System Data Analysis Foundation (SEADE)⁹.

The files of death certificates for the state of São Paulo for each year of the study were downloaded from the DATASUS website (<https://datasus.saude.gov.br/transferencia-de-arquivos/>). The files downloaded in DBC format were converted to DBF format, using the TABWIN software, and then analyzed using Excel software.

First, deaths with underlying causes of HCC, line (d) of the death certificate, code C22.0 of the ICD-10, were selected. Second, deaths due to HCC that appeared in the other lines of the certificate (consequential and contributing causes) and that were not included in the underlying cause were included.

In the next stage, deaths due to HCC that presented HBV and HCV codes (B18.0 – chronic HBV with Delta agent; B18.1 – chronic HBV without Delta agent; B18.2 – chronic HCV) in all lines corresponding to the causes of death were selected. Therefore, deaths due to HCC associated with viral hepatitis were considered, all deaths that had HCC in any line of causes of death and that simultaneously presented HBV or HCV mentioned in the declaration.

Generalized linear regression models were constructed using the Prais–Winsten method in the software Stata version 15, considering the significance level of 5%.

The time series of age-standardized mortality rates were represented in line graph format, constructed in Microsoft Office Excel 2013. To quantitatively estimate the time trends of mortality rates in the analyzed period, the formula of annual percentage change (APC) was used. The mortality coefficients were age-standardized by the direct method, using as reference the population of the 2010 census of the state of São Paulo.

A descriptive analysis of the sociodemographic characteristics of deaths was carried out according to the following variables: sex, age group, color, and schooling. Descriptive variables were analyzed by absolute and relative frequencies and by Pearson's chi-square test or Fisher's exact test, considering the significance level of 5%.

Maps were built with the spatial distribution of mortality rates, using SIG QGIS software version 3.4. The spatial unit of choice was the Regional Health Department (DRS), responsible for the management of Health Care of the State Department of Health at the regional level. The deaths were geocoded and described according to the DRS of residence, considering the following 3-year period: 2009–2011, 2012–2014, and 2015–2017.

Secondary public domain databases were used, without the use of any nominal data that could allow the identification of the subjects. Therefore, the ethical aspects of the research with human beings in force in resolution no. 466 of December 12, 2012, of the National Health Council were respected.

RESULTS

From 2009 to 2017, 2,499,738 deaths were found in the state of São Paulo. Among these, 5,870 had HCC as the cause of death, with 5,217 (88.9%) presenting HCC as the underlying cause of death and 653 (11.1%) mentioning HCC in the other lines of the death certificate (consequential causes and contributors of death).

Among the deaths due to HCC, 1,545 had HBV or HCV as an associated cause of death, that is, 26.3% (1,545 / 5,870) of deaths due to HCC were attributed to HBV or HCV.

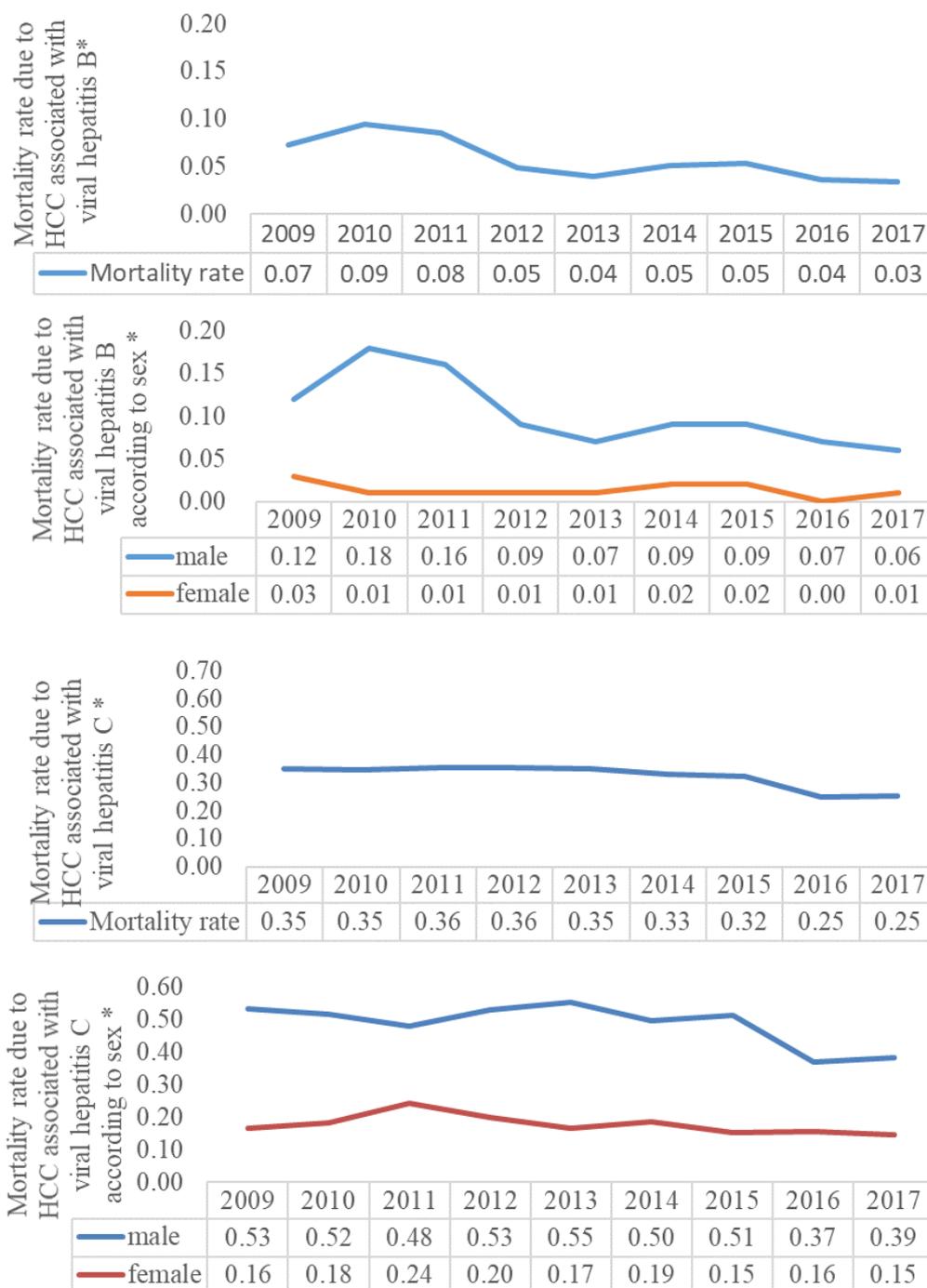
There were 1,306 (22.2%) deaths due to HCC associated only with HCV and 226 (3.9%) associated only with HBV, meaning there was a higher proportion of deaths due to HCC attributed to HCV when compared to HBV. Only 13 (0.2%) deaths due to HCC were associated with both viruses (HBV and HCV).

Standardized mortality rates due to HCC associated with HBV showed a significant reduction in the analyzed period, from 0.07 per 100,000 inhabitants-year in 2009 to 0.03 per 100,000 inhabitants-year in 2017, with an annual decrease of 10.4% (95%CI -17.0 to -3.2) (Figure 1 and Table 1). It was also observed that these rates were higher in males (Figure 1).

Standardized mortality rates due to HCC associated with HCV showed a stationary trend in the analyzed period, from 0.35 per 100,000 inhabitants-year in 2009 to 0.25 per 100,000 inhabitants-year in 2017 (APC=-4.0; 95%CI -8.6 to 0.7) (Figure 1 and Table 1). It was also observed that these rates were higher in males (Figure 1).

Most deaths due to HCC associated with viral hepatitis were male (75.5%), with a higher proportion in cases associated with hepatitis B (87.2%), white (73.9%), in the age group of 50–59 years (35%). The same profile was observed when they were analyzed separately for each type of hepatitis (Table 2).

There was a predominance of deaths in white (73.9%), with a similar proportion when analyzed separately for each type of hepatitis. When analyzing the level of education, a



Source: Mortality Information System, São Paulo, 2019. *Per 100,000 inhabitants / year.

Age-standardized mortality rate – using as reference the population of the 2010 census of the state of São Paulo.

Figure 1. Time series of age-standardized mortality rates due to HCC associated with hepatitis B and C viruses, in the state of São Paulo, 2009–2017.

Table 1. Annual Percentage Change of age-standardized mortality rates due to hepatocellular carcinoma, associated with viral hepatitis, in the state of São Paulo, 2009–2017.

| | APC | LL 95%CI | LS 95%CI | TRENDS |
|----------------------|-------|----------|----------|------------|
| Hepatitis B | -10.4 | -17.0 | -3.2 | Descending |
| Hepatitis C | -4.0 | -8.6 | 0.7 | Stationary |
| Hepatitis B (male) | -10.2 | -18.1 | -1.6 | Descending |
| Hepatitis C (male) | -3.8 | -8.1 | 7.5 | Stationary |
| Hepatitis B (female) | -8.3 | -19.7 | 4.5 | Stationary |
| Hepatitis C (female) | -2.6 | -8.1 | 3.1 | Stationary |

LL 95%CI: Lower limit of 95% confidence interval. LS 95%CI: Superior limit of 95% confidence interval. Age-standardized mortality rate – using as reference the population of the 2010 census of the state of São Paulo. Source: Mortality Information System, São Paulo, 2019.

higher proportion of deaths was identified in the category of 8–11 years of study (22.1%), but the cases associated with hepatitis B were predominantly present in individuals with 4–7 years of study (21.2%). It is noteworthy that 18.9% of the analyzed deaths had the education variable left blank or ignored (Table 2).

It is noteworthy that the deaths due to HCC associated with viral hepatitis were different in relation to overall deaths regarding sex, age group, and schooling ($p < 0.001$).

When analyzing the difference in deaths due to HCC associated with hepatitis B and those associated with hepatitis C, it was found that in women the proportion of deaths due to HCC associated with hepatitis C is higher (26.6%) than in deaths due to HCC associated with hepatitis B (12.8%) ($p < 0.001$). Another important factor observed was the age difference between deaths, noting that the proportion of deaths in the age groups of 30–39 years and 40–49 years is only 0.8% and 8.7%, respectively, when refers to deaths due to HCC associated with hepatitis C. In relation to hepatitis B, there is a greater proportion of deaths, 3.1 and 17.7%, respectively, for the same age groups ($p < 0.001$), indicating that individuals affected by HCC associated with hepatitis B die earlier (Table 2).

Regarding the color variable, there was a higher proportion of deaths among whites both in deaths due to HCC associated with hepatitis B and in those associated with hepatitis C, with 65.5 and 75.5%, respectively. It was found that in people with yellow skin, the proportion of deaths due to HCC associated with hepatitis B is higher (5.3%) than in deaths due to HCC associated with hepatitis C (1.8%) ($p < 0.001$) (Table 2).

When performing the spatial distribution, the crude mortality rates due to HCC associated with HBV showed a decline over the study periods. In the first period, the highest rate was observed in the Regional Health Department (DRS) of Ribeirão Preto with 0.20 deaths per 100,000 inhabitants/year, followed by the DRS of Greater São Paulo, Botucatu, and São José do Rio Preto, with 0.12, 0.11, and 0.11 deaths per 100,000 inhabitants/year, respectively.

Table 2. Sociodemographic characteristics of deaths due to hepatocellular carcinoma associated with hepatitis B and C viruses, in the state of São Paulo, 2009–2017.

| Variable | Total* | | Hepatitis B** | | Hepatitis C** | | Hepatitis B and C | |
|------------------|-----------|------|---------------|------|---------------|------|-------------------|------|
| | (n=1,545) | | (n=226) | | (n=1,306) | | (n=13) | |
| | n | % | n | % | n | % | n | % |
| Sex | | | | | | | | |
| Female | 379 | 24.5 | 29 | 12.8 | 348 | 26.6 | 2 | 15.4 |
| Male | 1,166 | 75.5 | 197 | 87.2 | 958 | 73.4 | 11 | 84.6 |
| Age group | | | | | | | | |
| 20–29 | 4 | 0.3 | 3 | 1.3 | 1 | 0.1 | 0 | 0.0 |
| 30–39 | 17 | 1.1 | 7 | 3.1 | 10 | 0.8 | 0 | 0.0 |
| 40–49 | 153 | 9.9 | 40 | 17.7 | 113 | 8.7 | 0 | 0.0 |
| 50–59 | 541 | 35.0 | 78 | 34.5 | 458 | 35.1 | 5 | 38.5 |
| 60–69 | 481 | 31.1 | 52 | 23.0 | 424 | 32.5 | 5 | 38.5 |
| ≥70 | 349 | 22.6 | 46 | 20.4 | 300 | 23.0 | 3 | 23.1 |
| Color | | | | | | | | |
| White | 1,141 | 73.9 | 148 | 65.5 | 986 | 75.5 | 7 | 53.8 |
| Black | 89 | 5.8 | 21 | 9.3 | 66 | 5.1 | 2 | 15.4 |
| Brown | 223 | 14.4 | 38 | 16.8 | 181 | 13.9 | 4 | 30.8 |
| Yellow | 35 | 2.3 | 12 | 5.3 | 23 | 1.8 | 0 | 0.0 |
| Indigenous | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Blank or ignored | 57 | 3.7 | 7 | 3.1 | 50 | 3.8 | 0 | 0.0 |
| Schooling | | | | | | | | |
| None | 82 | 5.3 | 21 | 9.3 | 60 | 4.6 | 1 | 7.7 |
| 1–3 | 291 | 18.8 | 38 | 16.8 | 251 | 19.2 | 2 | 15.4 |
| 4–7 | 296 | 19.2 | 48 | 21.2 | 247 | 18.9 | 1 | 7.7 |
| 8–11 | 342 | 22.1 | 36 | 15.9 | 301 | 23.0 | 5 | 38.5 |
| ≥12 | 242 | 15.7 | 35 | 15.5 | 207 | 15.8 | 0 | 0.0 |
| Blank or ignored | 292 | 18.9 | 48 | 21.2 | 240 | 18.4 | 4 | 30.8 |

*Difference in the distribution by sex, age group and schooling of total deaths due to hepatocellular carcinoma associated with hepatitis B or C viruses in relation to the total number of general deaths ($p < 0.001$). **Difference in distribution by sex, age group and color of deaths due to hepatocellular carcinoma associated with hepatitis B in relation to deaths due to hepatocellular carcinoma associated with hepatitis C ($p < 0.001$).

Source: Mortality Information System, São Paulo, 2019.

In the second triennium, the DRS of Baixada Santista and São José do Rio Preto stood out with 0.14 and 0.13 deaths per 100,000 inhabitants/year, respectively, while in the third study period, the DRS of Barretos stood out, with 0.16 deaths per 100,000 inhabitants/year (Figure 2).

In relation to crude mortality rates due to HCC associated with HCV, in the first period, the highest rate was observed in the DRS of Ribeirão Preto with 0.60 deaths per 100,000 inhabitants/year, followed by the DRS of Greater São Paulo and São José do Rio Preto stood out, both with 0.48 deaths per 100,000 inhabitants/year and then the DRS of Baixada Santista with 0.34 deaths per 100,000 inhabitants/year. In the second triennium, the highest rates were found in the DRS of Baixada Santista (0.62 deaths per 100,000 inhabitants/year), Greater São Paulo (0.51 deaths per 100,000 inhabitants/year), São José from Rio Preto (0.44 deaths per 100,000 inhabitants/year), and Ribeirão Preto (0.36 deaths per 100,000 inhabitants/year). In the third study period, the DRS of Ribeirão Preto, Baixada Santista, and Greater São Paulo stood out with 0.52, 0.51, and 0.38 deaths per 100,000 inhabitants/year, respectively (Figure 2).

DISCUSSION

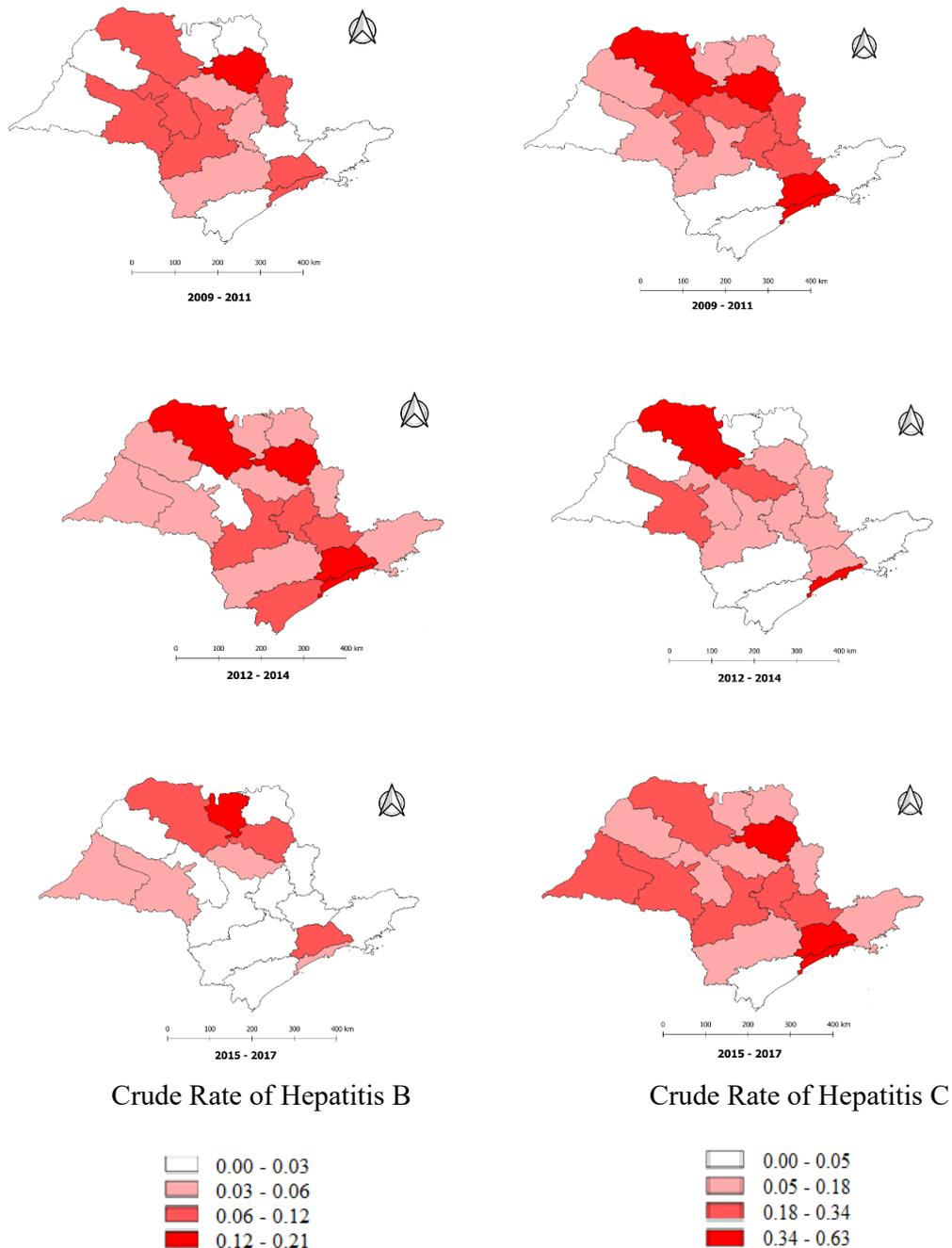
A higher proportion of deaths due to HCC associated with HCV was observed (22.2%) when compared to HBV (3.9%). The mortality rate due to HCC associated with hepatitis B showed a downward trend. However, the mortality rate due to HCC associated with hepatitis C showed a steady trend in the analysis period. The spatial distribution revealed a heterogeneous pattern of mortality rates due to HCC associated with viral hepatitis in the state of São Paulo.

The study by Fassio et al. on the etiology of HCC in Argentina concluded that the main etiological factors found in 551 studied HCC cases were alcohol (33%), HCV (32.8%), and HBV (10%)¹⁰. These results coincide with those obtained in this study, which found a higher proportion of deaths due to HCC associated with HCV and a lower proportion associated with HBV.

Similar to the results of this study, Sato et al. showed a downward trend in mortality from hepatitis B in the period from 2002 to 2016¹¹, as well as data from the state of São Paulo showing a rate reduction in hepatitis B detection from 9.41 cases per 100,000 inhabitants in 2009 to 7.56 cases per 100,000 inhabitants in 2014¹².

It is suggested that the decrease in mortality rates due to hepatitis B in our country can be attributed in part to vaccination, with a decrease in prevalence; the measures recommended by preventive actions against HIV infection, initiated in the 1980s, as observed in other countries, may have influenced the reduction of these rates¹³⁻¹⁶.

These findings highlight that the prevention of primary liver cancer through the HBV vaccine has been showing successful results. The hepatitis B vaccine is highly effective and practically free of complications. As hepatitis B is a major cause of liver cancer in the world, vaccination prevents not only hepatitis but also cancer¹⁷. In this same sense, it is likely that



Source: Mortality Information System, São Paulo, 2019.

Figure 2. Spatial distribution of crude mortality rates due to hepatocellular carcinoma associated with hepatitis B and C viruses, according to the Regional Health Department of residence, in the state of São Paulo, 2009–2017 (per 100,000 inhabitants / year).

the reduction in mortality due to HCC associated with hepatitis B, observed in this study, is due to the high vaccination coverage.

Regarding HCC mortality associated with hepatitis C, a steady trend in mortality rates was identified in the analyzed period. In contrast, the study by Akinyemiju et al. shows that between 1990 and 2015, there was an increase in the incidence and mortality of liver cancer worldwide due to HCV¹⁸.

Mortality rates due to HCC associated with hepatitis B were higher in males. This observation can be explained by male sexual behavior, with men being more exposed to the virus¹⁹. The same behavior was observed in mortality rates due to HCC associated with hepatitis C in the study period, with higher rates in males. Similarly, there are findings that men have more attitudes that leave them more exposed to the virus, such as the use of injectable or inhalable drugs, drinking alcohol, and the practice of sexual intercourse without the use of condoms²⁰.

There was a predominance of deaths due to HCC associated with HCV in the age group of 50–59 years (35.1%). This fact may be associated with several factors, such as late diagnosis, long latency period of viruses, and the absence of signs and symptoms (which denote the silent character of this type of hepatitis)²¹.

Regarding the level of education, this study pointed out that the majority of deaths due to HCC associated with hepatitis B had from 4 to 7 years of study and the majority of deaths due to HCC associated with hepatitis C had from 8 to 11 years of study. The study by Gonçalves et al., carried out in the state of Pará, from 2010 to 2014, pointed out that most of the notified cases of hepatitis B and C (35%) had low education (elementary school), indicating the relationship between these individuals and the conditions of socioeconomic vulnerability of populations, which can favor the transmission of the disease²². However, two factors can be considered: the sociodemographic differences between the states of Pará and São Paulo and the low filling in of this field, a fact that may have caused a bias in this analysis, as found by Cruz et al. in their study carried out in the state of São Paulo²³.

In this study, when analyzing the color variable, it was observed that 65.5% of deaths due to HCC associated with hepatitis B were white. With regard to HCC deaths associated with hepatitis C, 75.5% were white. These results coincide with the study by Sato et al., carried out in the city of São Paulo, in which there was a predominance of deaths from hepatitis B and hepatitis C in white individuals¹² and diverge from the study by Oliveira et al., in which the majority of notified cases of hepatitis C in a hospital in Goiás (75.1%) were brown²⁴.

The DRS that presented the highest mortality rates due to HCC associated with hepatitis B or C over the 9 years of this study may be related to several factors, such as genetic, demographic, socioeconomic, cultural, and historical factors in the population studied. Other issues can be raised in relation to past failures in prenatal control; the quality of the transfused blood, causing a greater occurrence of injuries; change of residence for treatment in larger municipalities, with more structured health services; and other social and

behavioral factors, such as the diversity of partners and the early onset of sexual activity. It is considered that the urbanization of these areas can also influence mortality rates^{25,26}.

Chronic viral hepatitis has a great impact on patients infected with HIV/AIDS²⁷. According to information from the São Paulo State Secretariat of Health (2018), the Epidemiological Surveillance Group (ESG) of Santos, Barretos, São José do Rio Preto, Ribeirão Preto, and Capital had AIDS mortality rates above the state average (4.9 deaths per 100,000 inhabitants) in the year 2017²⁸. Thus, the DRS with higher rates of mortality due to HCC associated with viral hepatitis may be related to possible cases of coinfection in these regions.

The Metropolitan Region of Santos stands out in the AIDS epidemic, being one of the cities with the highest incidence rate in the state of São Paulo. This panorama would be related to the fact that the city, through its port, is included in the cocaine trafficking route to Europe and North America²⁹⁻³¹. These factors may be related to the prominence that the DRS of Baixada Santista presented over the 3-year period of this study.

A study carried out in a hospital in the city of Ribeirão Preto-SP showed a prevalence of HIV/HBV of 20.4%³². These results may be related to the highlight that the DRS of Ribeirão Preto presented in this study.

Souto et al. evaluated the contribution of different parenteral routes of exposure to hepatitis C, including samples from nine cross-sectional studies, with a total of 3,910 individuals, and confirmed the use of injectable drugs as the main risk factor for HCV³³.

The study by Passos et al., carried out in the Ribeirão Preto region, with 208 former athletes, showed that the high prevalence of hepatitis C among former athletes was associated with the previous use of injectable stimulants³⁴. This fact may explain the highlight that Ribeirão Preto DRS presented in this study, indicating that the use of injectable drugs in the past decades in this region may have contributed to the results found.

In this study, the DRS that presented the highest rates of HCC associated with hepatitis C may reflect social and behavioral problems, such as the large number of injecting drug users in these regions in the past decades.

A limitation of this study is the use of secondary data. It is necessary to consider that the time elapsed between the moment of infection by hepatitis B or C and the development of HCC usually takes decades, in other words, the interpretation of these data must be cautious, since it may reflect the diagnosis and treatment in regions with large medical centers, which does not mean that this was where the infection was acquired.

The reduction in the mortality rate due to HCC associated with hepatitis B shows an important advance in the control of the disease due to the immunization actions with the hepatitis B vaccine. However, the mortality rate due to HCC associated with hepatitis C has been stable over the study period, indicating the need for actions and measures to reduce these rates. In this sense, the increase in the detection of cases of hepatitis C, through the expansion of the offer of rapid tests or the serology for the population most vulnerable to the risk of infection, as well as for people aged 40 years and above and who may have been infected in the past decades, is an important strategy for diagnosis. In addition, the treatment

of affected individuals will contribute to the prevention and control of the disease, with the consequent reduction in cases and deaths due to HCC associated with hepatitis C.

The spatial distribution of deaths may contribute to the managers and professionals of the DRS, in the sense of raising hypotheses for more in-depth knowledge of their regions, based on these results.

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