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Time trends and geographic distribution of hepatocellular carcinoma in Brazil

An ecological study

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Abstract

The incidence of hepatocellular carcinoma (HCC) is increasing globally, and HCC is the fourth leading cause of cancer-related death. This ecological study aimed to investigate the time trends and geographic distribution of HCC in Brazil. Data from the Brazilian Health Public System were retrospectively collected from January 2005 to December 2018. Hospitalization and intrahospital lethality rates for HCC were stratified by age and sex. Hospitalization rates and associated lethality per 100,000 inhabitants in each municipality were included in a worksheet to build maps displaying the estimates and the geographic distribution of HCC. From 2005 to 2018, a total of 75,466 admissions for HCC were registered and the mean hospitalizations increased from 2.1 to 5.8/100,000 inhabitants (176%). The greatest increase occurred among patients older than 50, particularly in males above 70 years old. Prevalence rates increased throughout the country, with the highest levels detected in the South and Southeast. However, the increase was proportionally higher in the Northeast (377%), especially in municipalities not integrated into metropolitan regions. The HCC lethality rate remained relatively stable in both sexes, ranging from 21% to 25% (19%), but it was higher among older patients. The length of hospital stay did not differ between survivors and nonsurvivors throughout the study period. HCC hospitalizations are rising, particularly above 50 years of age and in rural areas, not paralleled by lethality rates. This suggests ongoing changes in environmental and socioeconomic factors in Brazil.

Abbreviations: HCC = hepatocellular carcinoma, ICD-10 = International Classification of Diseases 10th Revision, MR = metropolitan region.

Keywords: epidemiologic study, hepatocellular carcinoma, hospitalization rates, long-term analysis, mortality rates

1. Introduction

Hepatocellular carcinoma (HCC) is a tumor of the parenchymal cells of the liver and accounts for approximately 80% of all primary liver cancers. HCC represents the sixth most common neoplasm in the world and the fourth leading cause of cancer-related death.[1] The incidence is rising in many parts of the world, and the number of deaths attributed to HCC in the United States has increased in recent years, despite efforts to improve prognosis.[2] The incidence of HCC is particularly high in East Asia and Western Africa, but it is also increasing in several Western countries. Patients with HCC have an estimated average 5-year survival rate of approximately 20%.[3] However, approximately half of the patients are diagnosed at advanced stages with regional and distant disease, and the estimated 5-year survival can fall to less than 5% in these patients.[4] In most cases, HCC develops within an established background of chronic liver disease secondary to viral hepatitis, alcohol consumption, or nonalcoholic steatohepatitis, and therefore, it has a poor prognosis due to both the tumor itself and the severity of the underlying liver disease.

Regarding the global distribution, approximately 75% of liver cancers occur in Asia, with China accounting for over 50%. The lowest incidence rates occur in the countries of Northern Europe, the Middle East, Oceania, and North and South America, whereas countries in Central Europe have

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The authors have no conflicts of interest to disclose.

Data from the Health Informatics Department of the Brazilian Ministry of Health (DATASUS) are freely available on the Internet at http://www2.datasus.gov.br/DATASUS. DATASUS registries include hospital admission and discharge information, medical procedures and mortality, reference tables, and demographic data (age, sex, municipality) collected by the Instituto Brasileiro de Geografia e Estatística (IBGE; Brazilian Institute of Geography and Statistics).

This manuscript, including related data and tables, has not been previously published and is not under consideration elsewhere.

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intermediate rates.[4] Between 2003 and 2007, liver cancer incidence increased in many areas of the world, notably India, Oceania, and North and South America, as well as in many European countries. In contrast, in more recent years, incidence rates have declined in some Asian countries, Spain, and Italy.[5,6]

Currently, very limited information is available regarding HCC in Brazil, basically derived from surveys performed in referral centers.[7–9] In a previous study concerning HCC demographics in South America, the analysis of a cohort including data from centers in Colombia, Argentina, Ecuador, Uruguay, Peru, and Brazil revealed similarities with North America, Japan, and Europe in terms of age and risk factors. It is notable, however, that 40% of the patients in the study were from Brazil, but the data were obtained from only 2 centers in the country.[10] In a recent review on the epidemiology of HCC in Latin America, the authors point to sociocultural heterogeneities and economic disparities of the region, as potential barriers to addressing this important health issue. In addition, the study suggests that a considerable proportion of patients may still be diagnosed in the later stages of the disease.[11] The same group of investigators performed a transversal survey on HCC using data from individual health centers and detected a differential distribution of the disease among the Brazilian macroregions.[12] Brazil is a continental country with more than 5000 municipalities spread throughout 5 macroregions, with particular urbanization patterns and geographic characteristics. Hence, it is expected that unveiling the epidemiology of HCC in Brazil will be instrumental for elucidating risk factors and potential causes and may lay the groundwork for preventive strategies in public health. Therefore, this study aimed to investigate the geographic distribution and time trends of hospitalizations and intrahospital lethality for HCC in Brazil to characterize areas with differential risks and outcomes of HCC.

2. Materials and Methods

2.1. Ethical considerations

Ethical approval was waived by the local Ethics Committee of the University Hospital Clementino Fraga Filho, of the Federal University of Rio de Janeiro, given the retrospective nature of the study investigating a population-based health and disease registry, anonymously archived.

2.2. Data source

Data from the Health Informatics Department of the Brazilian Ministry of Health (DATASUS) registry (http://www2.datasus.gov.br/DATASUS) were retrospectively collected, similar to previous studies from our group.[13,14] DATASUS is a population-based health and disease registry with open access through the Internet and includes information on medical procedures, hospital admission and discharge, mortality, and demographic variables, covering approximately the entire population. All archival data are completely anonymous and do not allow for the identification of individual subjects. In this study, we used records from hospitalizations (hospital admissions) for HCC.

2.3. Study design, population, and variables

To investigate the geographic distribution and temporal changes of risk factors potentially involved with the development of HCC, we conducted an ecological study utilizing data from the DATASUS platform. Ecological studies constitute observational investigations usually applied at the population level to estimate the incidence and prevalence of a particular disease and its behavior in space and in time.[15] Records of hospitalizations for HCC (inpatient records only) obtained from the DATASUS registry from January 2005 to December 2018 were retrospectively searched according to the HCC classification in the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10). Three ICD-10 codes were considered for the search: C22-0 (hepatocellular carcinoma/hepatoma), C22-7 (other specified carcinomas of the liver), and C22-9 (liver, unspecified). The study period was selected considering the most recent and consistent data available. Therefore, the inclusion criteria for this study considered the preselected ICD classifications for HCC, within the predefined time range. The electronic medical record retrieved from DATASUS requires the presence of ICD classifications for each patient, as a major reference in the health system and for billing purposes. For this study, we worked with the ICD classifications attributed upon the hospital discharge to avoid missing changes or updates in diagnoses during the hospitalization period. The data analyzed included information on age, sex, the town of residence at the time of hospital admission, length of hospital stay, and death. For practical purposes, the date of diagnosis was defined as the date of hospital admission. Hospitalizations and intrahospital lethality for HCC were stratified by age and sex. Age groups were stratified as 20–49 years, 50–69 years, and 70 years or older. In this ecological study, we used an exploratory approach to assess the effects of the variables available within the system database. The results from the exploratory analysis of hospitalization rates and associated lethality per 100,000 inhabitants in each municipality were included in a worksheet to build maps displaying the estimates and the geographic distribution of HCC in the country.

2.4. Statistical analysis

For the statistical analysis, we used the same approach as in previous studies from our group.[16,17] HCC hospitalization rates were determined after correcting for the total number of available hospital beds and divided by the resident population in Brazil annually, from 2005 to 2018. Estimates of the resident population were obtained from the Instituto Brasileiro de Geografia e Estatística (IBGE; Brazilian Institute of Geography and Statistics) projections. Simple linear regression was applied to estimate temporal trends in HCC hospitalizations and lethality by age and sex using Microsoft Excel Software (Microsoft Excel for Mac 2011, Version 14.4.9, 2010; Microsoft Corp, Redmond, Wash). Statistical analysis was performed using the statistical software package IBM SPSS for Windows (Version 20; SPSS Inc, Chicago, IL). Exploratory procedures were applied to the data, and summary descriptive statistics and graphical displays were generated by Tabwin 3.2 (Tab for Windows 3.2, free software that allows organization of multiple applications into grouped tabs, freely available at http://www2.datasus.gov.br/DATASUS). All tests were 2-tailed, and statistical significance was set at a P value of less than .05. The statistical methods of this study were reviewed by Jessica P Moreira and Ronir R Luiz, from the Institute of Public Health Studies, Federal University of Rio de Janeiro, and coauthors in this article.

3. Results

3.1. Hospitalizations for HCC

Brazil's Unified Health System (SUS – Sistema Único de Saúde) is one of the largest public health systems in the world, with more than 200 million people who rely almost exclusively on its health services. SUS hospital beds account for almost 75% of the total number of hospital beds, while the remaining beds are from hospitals linked to the SUS or private units (Figure S1, Supplementary Digital Content, http://links.lww.com/MD/H331).

During the study period, hospitalizations for HCC in Brazil increased from 2891 cases in 2005 to 8297 cases in 2018, while the fatality rate increased from 21% to 25%. The estimated hospitalization rates, adjusted according to the number of available hospital beds, increased from 2.1 in 2005 to 5.8 in 2018 per 100,000 inhabitants (Table 1).

During the study period, the overall hospitalization rates for HCC per 100,000 inhabitants increased from 2.2 to 6.9 in men and from 2.0 to 5.8 in women. These data show a proportionally higher increase in the hospitalization rates for HCC in men than in women (Fig. 1A).

Considering the age distribution of HCC, the hospitalization rates were very low for the first group aged 20 to 49 years (<1.7/100,000 in 2018), intermediate for the second group aged 50 to 69 years (23.4/100,000 and 12.2/100,000 for men and women, respectively, in 2018) and higher for those aged ≥ 70 years, irrespective of sex. The higher hospitalization rates among males were proportionally greater among older individuals (Fig. 2 and Table 2).

3.2. Lethality of HCC

The global intrahospital lethality rates associated with HCC increased from 21% in 2005 to 25% in 2018 (Tables 1 and 2). However, HCC intrahospital lethality rates estimated from DATASUS were not affected by sex during the period from 2005 to 2018; they increased in both sexes in a similar way (Fig. 1B), and proportionally more among older individuals (Fig. 3).

3.3. Length of hospital stay

Comparing survivors and nonsurvivors of HCC, the median hospitalization time in days did not differ between 2005 and 2018, but there was a tendency for a reduction in the length of the hospital stay among the HCC survivors in the last year of the study period (5.0 and 5.0, respectively; and 3.0 and 5.0, respectively) (Table 3).

3.4. Geographic distribution of HCC

Data collected from the DATASUS platform included the patients' residential addresses. By the time of the study, all 5565 municipalities distributed in 27 federative units and grouped in 5 macro-regions (North, Northeast, Central-west, Southeast, and South) were considered. In all 5 macro-regions of Brazil, the hospitalizations for HCC increased over the 14 years, with the highest rate of increase occurring in the Northeast region (Figs. 4 and 5). Although the lethality increased in all regions, the rates did not parallel the HCC hospitalizations, particularly in the Northeast, where the increase was the least expressive in the period (Figs. 4 and 6).

Taking into account the economic and demographic disparities of Brazil, a large and unequal country, data on hospitalizations and intrahospital lethality for HCC were reviewed based on the demographic and commuting patterns of Brazilian municipalities. In the model utilized in this study, the municipalities were classified, considering the population and demographic density, into rural small (<50,000 inhabitants or <80 inhabitants/km), rural medium (≥50,000 inhabitants or ≥80 inhabitants/km, even if the population is <50,000 inhabitants) and true urban centers (>100,000 inhabitants). Because the Brazilian population tends to aggregate in large urban centers, searching for better economic opportunities, a second classification based on the size of the municipalities was also applied to the model. As a result, the municipalities were divided into large, medium, and small and whether they were integrated into metropolitan regions or not.[18]

Metropolitan integrated municipalities had the highest HCC hospitalization rates, both in 2005 and 2018 (2.5 and 6.0, respectively), primarily in the large municipalities (2.6 and 6.1, respectively). These rates were higher than the average rates for the whole country (2.1 and 5.6, respectively). In the nonintegrated metropolitan municipalities, HCC hospitalization rates were 1.7 in 2005 and 5.2 in 2018. From 2005 to 2018, HCC lethality rates increased by 19% in metropolitan integrated municipalities (21%–25%) and 14% in metropolitan nonintegrated municipalities (22%–25%) (Table 4).

4. Discussion

To our knowledge, this is the first study to consider Brazilian nationwide information on HCC that had been collected from an official source of the Ministry of Health. Data obtained from January 2005 to December 2018 indicated that the overall HCC hospitalizations increased by more than a hundred percent during these 14 years, while the lethality rate increased by less than twenty percent. In addition to the clear male predominance in HCC, we detected an increase among individuals older than 50 years of age, particularly among individuals older than 70 years of age. The geographic distribution of HCC revealed a higher concentration in the South, but the relative increase was greater in the Northeast region.

Table 1

Hepatocellular carcinoma (HCC) hospitalizations and lethality rates in Brazil from 2005 to 2018.

Year	Number of hospitalizations	Number of deaths	Hospitalizations per 10^5 inhabitants	Lethality rate (%)	Hospitalizations adjusted by hospital beds per 10^5 inhabitants	Hospital beds (SUS) (%)
2005	2891	619	1.6	21	2.1	75.26
2006	3022	616	1.6	20	2.2	75.04
2007	3122	733	1.6	23	2.2	75.25
2008	3107	705	1.6	23	2.2	74.52
2009	3944	1035	2.1	26	2.8	73.64
2010	4132	1049	2.2	25	3.0	72.92
2011	4920	1143	2.6	23	3.5	72.33
2012	5787	1321	3.0	23	4.2	71.84
2013	6565	1515	3.3	23	4.6	71.25
2014	6745	1594	3.3	24	4.7	70.86
2015	7362	1845	3.6	25	5.1	70.97
2016	7496	1784	3.7	24	5.2	70.53
2017	8076	1887	3.9	23	5.6	69.54
2018	8297	2111	4.0	25	5.8	69.13

SUS = Brazilian Unified Health System.

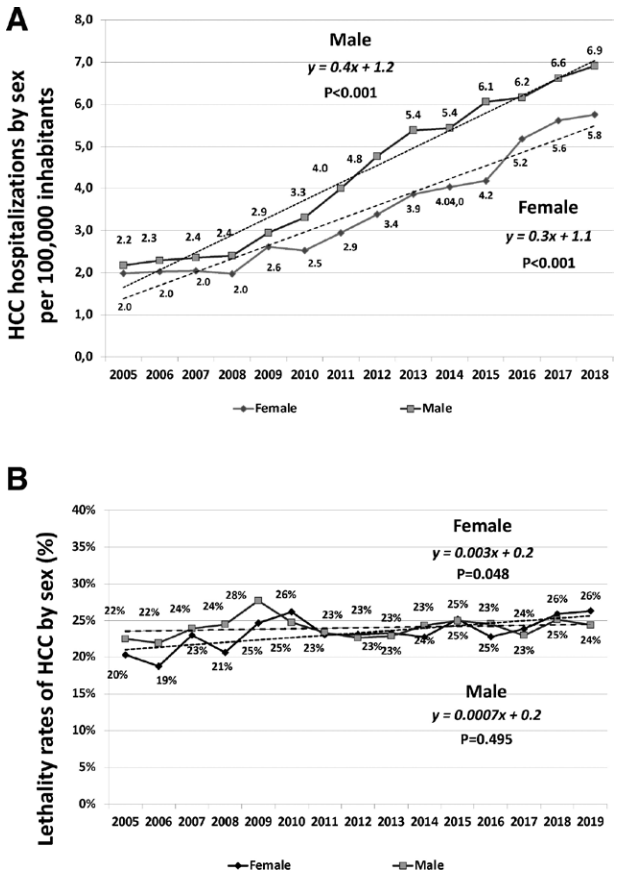

Figure 1. Hepatocellular carcinoma hospitalizations (A) and intrahospital lethality (B) by sex, in Brazil from 2005 to 2018. Rates were calculated by dividing the total number of hospitalizations by the resident population and adjusted according to the total available hospital beds.

Cirrhosis is estimated to affect 1%–2% of the global population, causing over 1.2 million (2% of total) deaths in 2013, an increase of 47% since 1990.[19] In Brazil, although data on cirrhosis are still scarce and usually stem from limited surveys, most cases have been attributed to chronic viral hepatitis C and B, and alcohol consumption.[20–22] Nonetheless, the continuous worldwide rise of non-alcoholic liver disease (NAFLD), which is becoming one of the most common causes of liver diseases, and associated with the development of HCC,[23,24] also emerges as a relevant cause of chronic liver diseases and HCC in Brazil.[25,26] Despite the clinically unequivocal factors predisposing patients to cirrhosis and HCC, cancer prevention in this setting remains a difficult and urgent task, as demonstrated by the poor prognosis of HCC (5-year survival rate of <15%), which encompasses a wide variety of medical interventions.[27]

The global pattern of HCC incidence is related to the presence of the major risk factors, its endemicity, and the length of time that the risk factors have been present in the human population. HBV virus and alcohol consumption have usually been regarded as the most common factors underlying the development of HCC, along with HCV and, until recently, obesity, diabetes, and metabolic syndrome as risk factors for chronic liver disease. Nevertheless, the magnitude of HCC risk for emerging populations, including patients with noncirrhotic NAFLD and those who have been cured of HCV, has yet to be determined, and screening strategies for these populations have not been established.[28] In a multinational study conducted in 14 centers in 6 South American countries where 40% of the patients (540) were from Brazilian centers, the most common risk factor for HCC was HCV infection (48%), followed by alcoholic cirrhosis (22%), HBV infection (14%), and NAFLD (9%).[10]

In this study, the highest hospitalization rates of HCC occurred among older individuals. As the population ages, individuals are more likely to be exposed to and accumulate concomitant behavioral, lifestyle, or environmental risk factors, and the likelihood of developing cirrhosis increases.[29] Brazil, like other developing countries, is dealing with a rapidly growing aging population and has the sixth-largest population of elderly people in the world. People over 60 years old correspond to 8% of the general Brazilian population, with a projection of 32 million people by 2020.[30,31] Increasing age is a well-established risk factor for HCC development, and in general, patients from areas with high prevalence rates of HCC tend to be younger, whereas patients from areas with relatively low HCC prevalence rates tend to be older at diagnosis.[4,32] This phenomenon may be a consequence of age at infection and the duration of infection with either HBV or HCV.[33,34] In Brazil, where HCV is a major risk factor, infections seem to occur later in life. In a recently proposed HCC prediction model for HCV-infected patients, age was the only host variable that was included in the final model, underscoring its importance as a risk factor for HCC.[2,29]

In terms of sex, the results of this study are consistent with the worldwide prevalence rates of HCC, which indicates a higher prevalence among males. The sex difference in HCC, with males having a 2- to 4-fold higher prevalence than females,[4,35] is usually attributed to differences in exposure to risk factors, such as viral hepatitis, alcohol abuse, cigarette smoking, and elevated iron stores. However, even when controlling for these variables, significant differences in the prevalence of HCC between the sexes remain.[34] Taken together, these data support the idea that the androgen axis promotes HCC in males, whereas the estrogen axis protects females from HCC.[36] It is interesting to highlight that while hepatitis B is not the major etiology for cirrhosis in the country, this study shows a proportionally higher increase among males. Nevertheless, when considering the population above 70 years old, the study results revealed a progressive increase in the hospitalization rates for HCC throughout the 14 years both in males and females.

Considering the intrahospital lethality associated with HCC, the rates observed from 2005 to 2018 did not show relevant differences based on age or sex. The high rates of HCC observed in the older population are not necessarily paralleled by a proportional increase in lethality (i.e. the HCC cases in this age group do not seem to be more aggressive).

Regarding geography, Brazil is a continental and heterogeneous country, and there are huge demographic and developmental differences among the 5565 municipalities and 5 large macro-regions. In this study, the Northeast region had the highest increase in hospitalization rates for HCC, followed by the Southeast and South macroregions. Although the highest development indices are in the South and Southeast regions, it is important to note that a remarkable increase in health services, including transplant centers, occurred in the Northeast during this period. Particularly in the Northeast region, 9 transplant centers in 2005 performed 124 liver transplants (12.6% liver transplants in 2005), and in 2018, 10 transplant centers performed 352 liver transplants. This increase was probably related to training more hepatologists in the care of cirrhotic patients, and better surveillance and imaging screening for HCC and confirms that these centers became much more active in these 14 years compared to other regions.[37,38] Considering the highest lethality rate in the North region, which is less developed in Brazil, it is plausible to speculate that the specialized care necessary to treat cirrhotic HCC patients is still suboptimal. The North region is also the area where there is the highest prevalence of HBV in the country (14.7%),[39] which could be a reflection of suboptimal rates of HBV immunization in the region.

Because of the heterogeneity observed among the macroregions of the country, we performed an additional analysis in relation to the demographic distribution based on the stratification

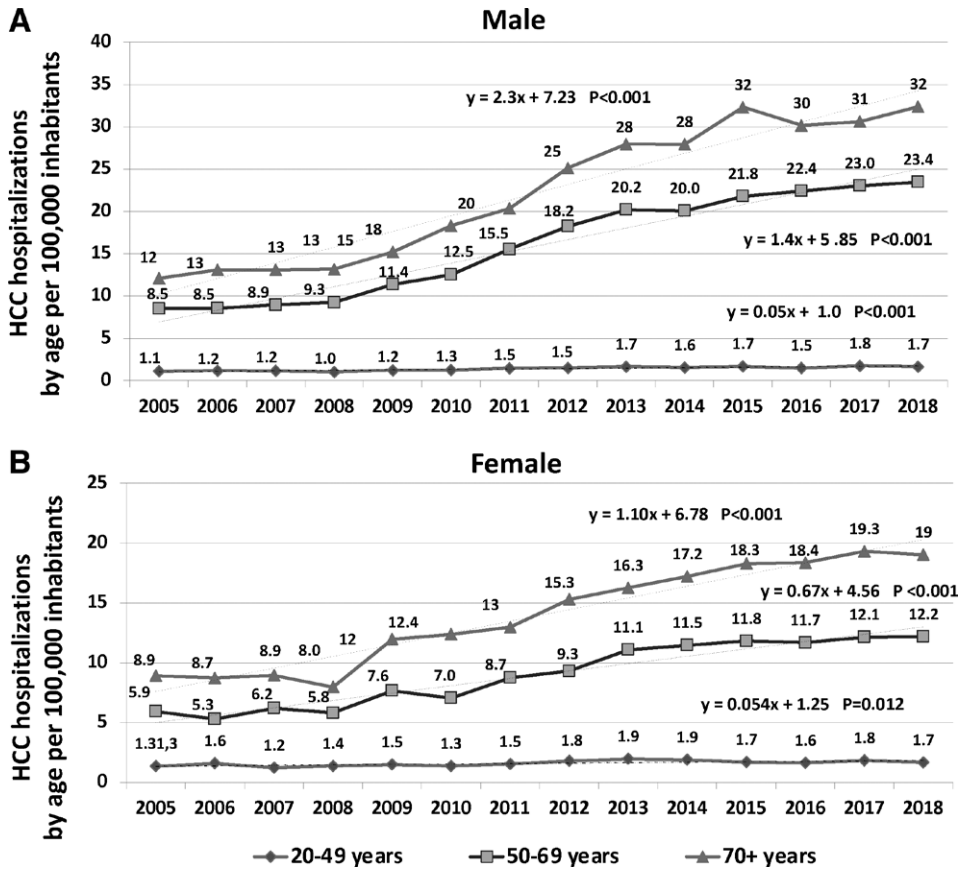

Figure 2. Age-stratified HCC hospitalizations by sex, estimated in Brazil from 2005 to 2018. Rates were calculated by dividing the total number of hospitalizations by the resident population and adjusted according to the total available hospital beds.

Table 2

Age-adjusted hospitalizations and intrahospital lethality rates for HCC in Brazil and corresponding changes in rates from 2005 to 2018.

	Age (y)	2005	2018	Changes in rates (%)
Hospitalizations	20–49	1.3	1.7	32
(per 100,000)	50–69	8.1	17.5	116
	>70	11.6	24.6	112
Lethality (%)	20–49	16.9%	18.3%	9
	50–69	25.7%	24.3%	–5
	>70	30.3%	33.5%	11

of the population size and density. With this approach, we identified geographic shifts in the hospitalizations for HCC not only from the South toward the Northeast but also from urbanized to rural areas. Our data showed that although there is a growing populational concentration in large urban centers, greater increases in hospitalizations for HCC were observed in rural municipalities, not paralleled by proportional increases in lethality rates. These results appear to highlight ongoing alterations in the socioeconomic environment, also involving less developed regions and municipalities. In fact, remarkable transformations have been seen in Brazil in the last few decades, with shifts from predominantly agricultural to industrial activities and a continuous migratory flow predominantly from rural to urban areas.[40] In addition, lifestyle changes have been noticed in Brazilian society, for example, favoring a predominantly high-caloric Westernized diet, instead of the traditional fiber-rich diet, even in small municipalities and rural areas.[41] These changes have been accompanied by the increase in overweight, obesity, and diabetes,[42–44] temporally overlapping with the rise of hospitalizations for HCC in the country observed in the current study. On the other hand, the relative stability of lethality rates of HCC observed in rural areas may suggest improvements in the quality and decentralization of health services during the period analyzed.

In a recent study, Nutini et al demonstrated the distribution of distinct HCV genotypes in Brazil. Genotype 3 was more prevalent in the South region, while genotype 1A was the most prevalent overall.[45] In terms of HCV pathogenicity, it is well established that genotype 3 is associated with an increased risk for the development of steatosis, fibrosis, and HCC. A previous study has shown that individuals infected with genotype 3 have a 31% higher risk of developing cirrhosis and 80% higher risk of developing HCC than individuals infected with genotype 1.[46] The differential distribution of HCV genotypes in the country may explain the findings of higher hospitalizations and lethality rates in the South region. Although currently, the more efficient

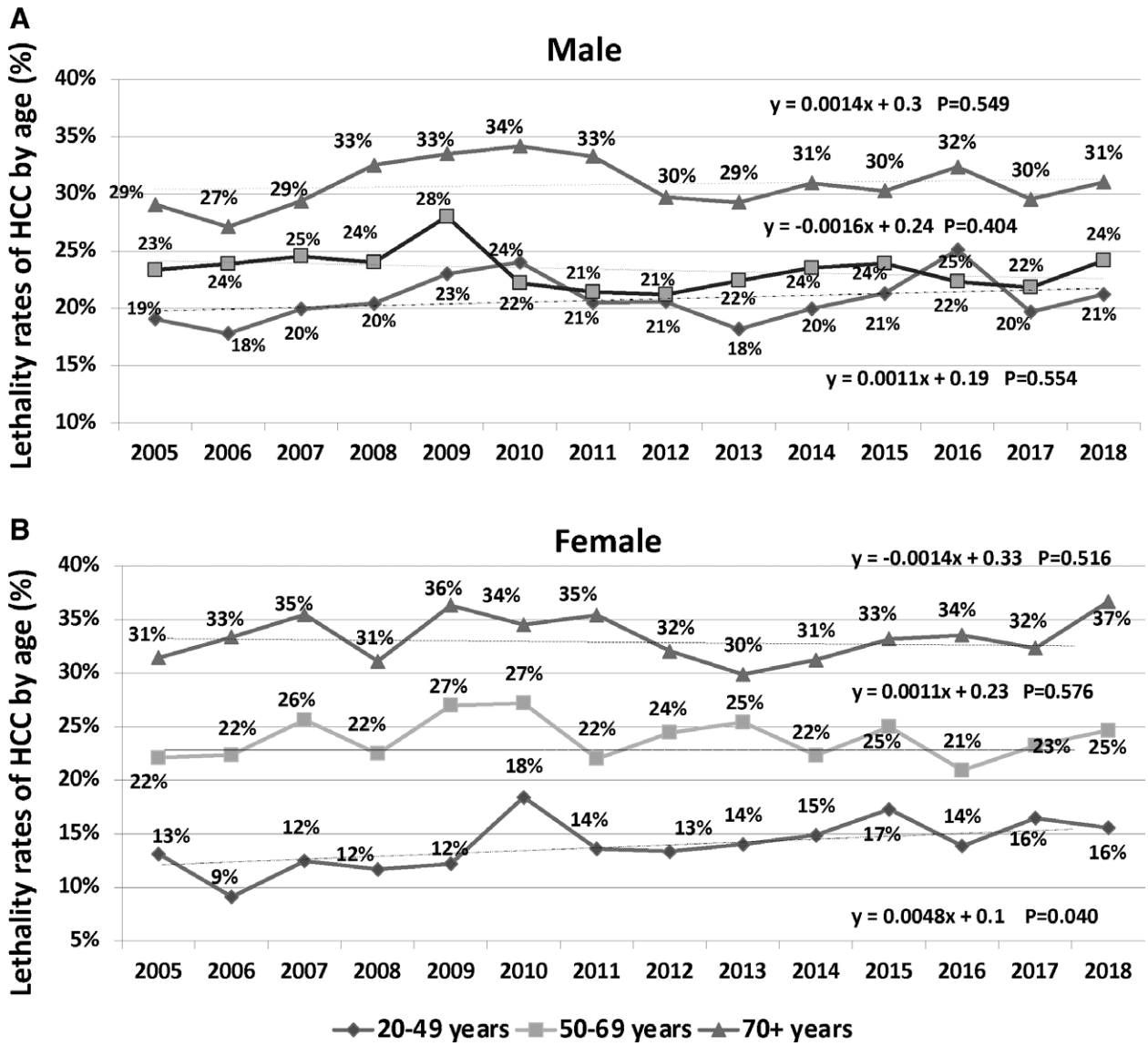

Figure 3. Age-stratified HCC lethality rates (%) by sex, estimated from intrahospital deaths in Brazil from 2005 to 2018.

Table 3

Length of hospital stay (in days) for HCC, considering both deaths and nondeaths, in 2005 and 2018.

	2005					2018				
Deaths	**Mean**	**SD**	**Median**	**Minimum**	**Maximum**	**Mean**	**SD**	**Median**	**Minimum**	**Maximum**
No	8.2	9.6	5.0	0	99	5.6	6.8	3.0	0	88
Yes	9.4	11.8	5.0	0	114	7.1	8.4	5.0	0	104

HCC = hepatocellular carcinoma, SD = standard deviation.

treatment of HCV is undoubtedly relevant for the prevention of HCV-related HCC, the period covered by this study was still unable to detect the potential benefits of these recent advances. Nonetheless, a critical understanding of the differential distribution and lethality of HCC in Brazil will be fundamental for defining future health policies. Given the size and heterogeneity of the country, it is expected that high-quality information from municipalities might guide in terms of vaccination, improvements in access to diagnostic methods and medication, and investment in equipment and personnel for hospital procedures and transplantation.

Evidence indicates that NAFLD and nonalcoholic steatohepatitis (NASH), which are frequently accompanied by obesity, are associated with the development of HCC.[24] Both overweight and obesity also exhibited increasing trends in the Brazilian population from 2008 to 2013 according to a population-based cross-sectional study based on the VIGITEL databases (National System of Surveillance of Chronic Diseases by

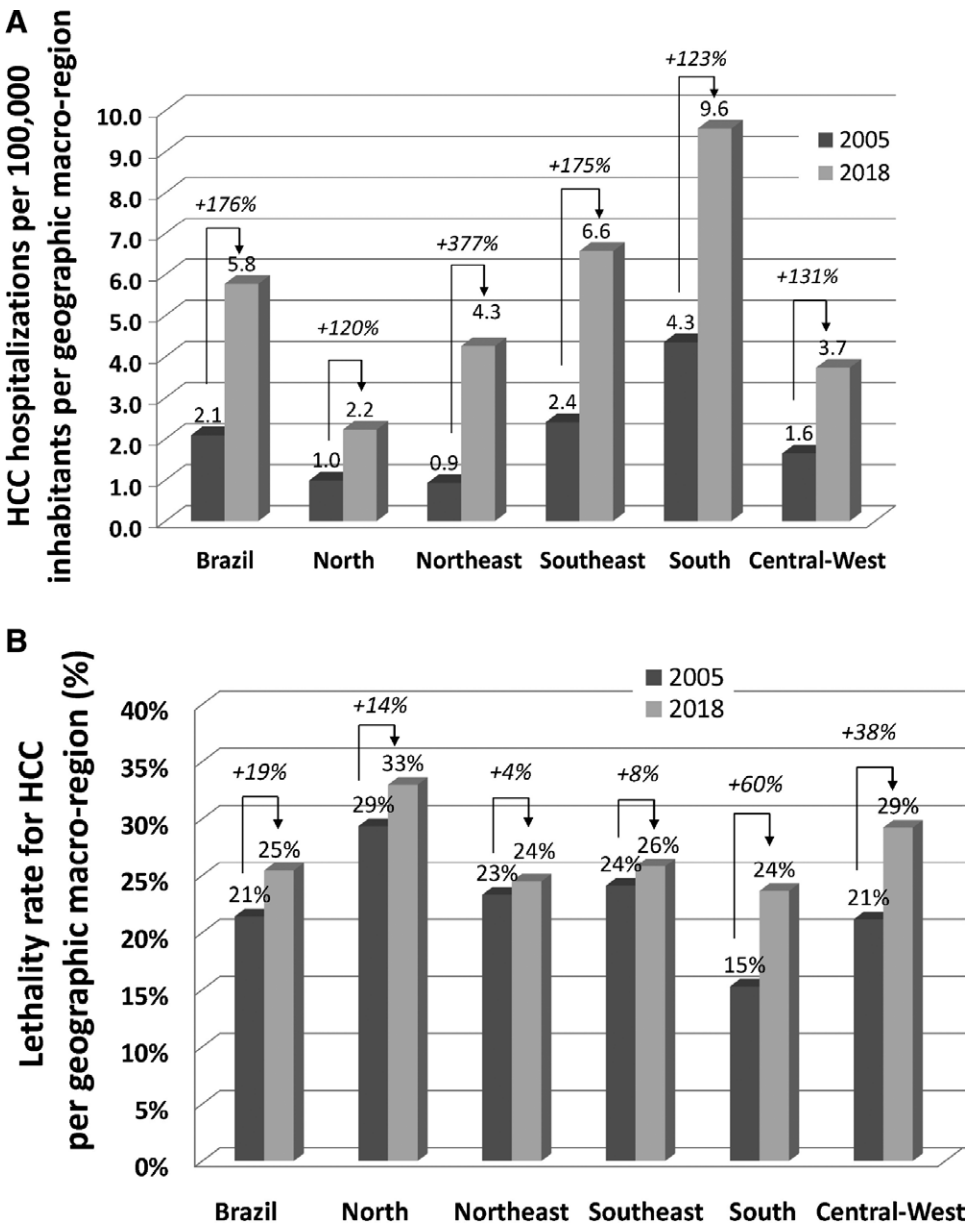

Figure 4. HCC hospitalizations (A) and intrahospital lethality (B) in the 5 Brazilian macroregions in 2005 and 2018. Rates were calculated by dividing the total number of hospitalizations by the resident population and adjusted according to the total available hospital beds.

Telephone Survey).[47] In particular, many studies have found an association between HCC risk and diabetes, obesity and metabolic syndrome, and its hepatic manifestation, NAFLD.[48–50] Although the relative risk for the development of HCC is greater in those with HCV or HBV infections, the progressively higher prevalence of NAFLD in the general population renders it an increasingly important cause of HCC.[51] Moreover, as the prevalence of diabetes in the world and, in developing countries, in particular, is expected to increase by 69% by the year 2030, the prevalence of HCC will likely grow in parallel.[52] Currently, obesity accounts for approximately 16% of HCC cases in Europe.[53] In contrast, both obesity and/or diabetes account for approximately 37% of HCC cases in the United States.[54]

The recently published GLOBOCAN estimates indicate that liver cancer represents the sixth most commonly diagnosed cancer and the third leading cause of cancer-related death in the world in 2020. The results continue to show 2 to 3 times higher rates among men than among women in most regions, however with a remarkable heterogeneous distribution.[55] In this study, the hospitalization rates for HCC appear to be substantially lower than the GLOBOCAN estimates of HCC prevalence in Brazil. However, our study analyzed exclusively hospital records for HCC and, in contrast to GLOBOCAN, which analyzes liver cancer in general, our study focused on HCC, specifically. Moreover, different methodologies and distinct sources of information utilized in each study may render data practically impossible to compare directly. Although these estimates from GLOBOCAN are critically important in terms of world health, they may not be sufficient to unveil the complexity and peculiarities of specific regions or countries. This might be particularly relevant when analyzing large territories where geosocial aspects show great contrasts. Different from other studies using transversal data from referral centers or local surveys, this ecological approach allowed us to cover the whole territory using a single electronic database, the largest available in the country comprising information on health, including HCC. In this regard, considering the predefined settings used for the analysis based on ICD records,

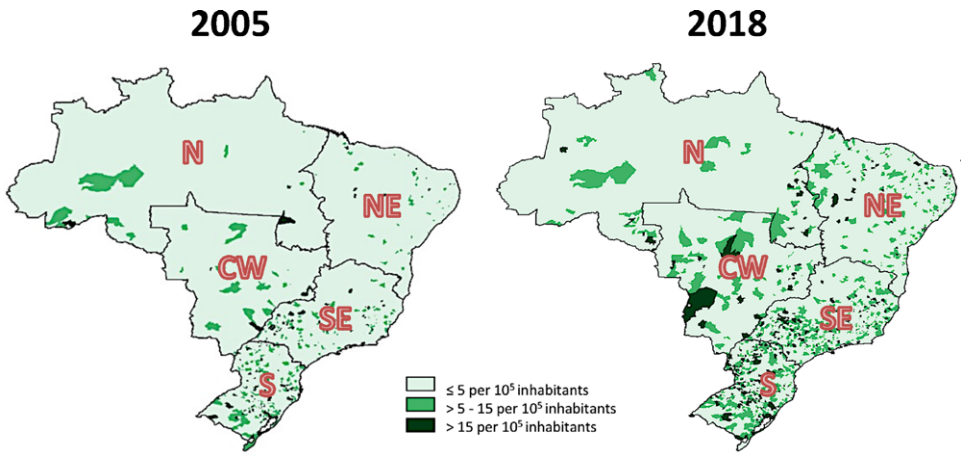

Figure 5. Geographic distribution of hepatocellular carcinoma in Brazil according to the municipal hospitalization rates (per 100,000 inhabitants) in 2005 and 2018. Standardized rates defined the following 3 ranges: <5, 5–15, and >15. CW indicates Central West; N, North; NE, Northeast; S, South; SE, Southeast.

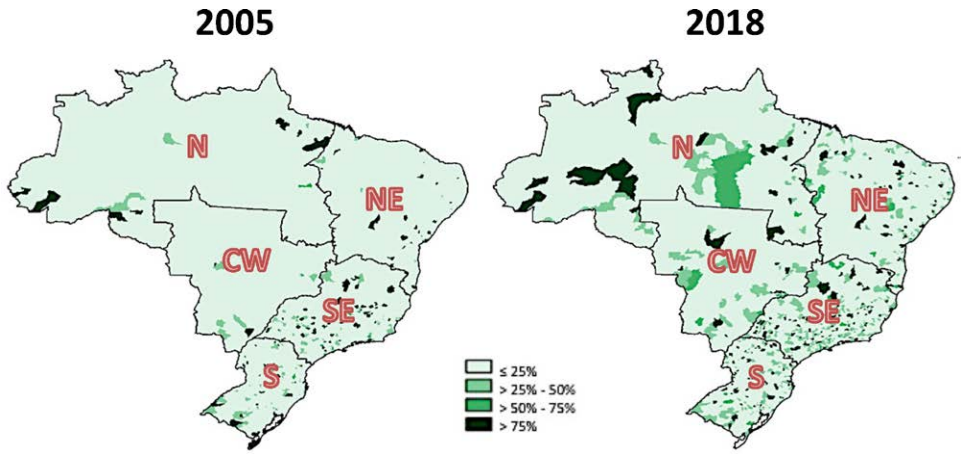

Figure 6. Geographic distribution of hepatocellular carcinoma lethality in Brazil according to municipal rates of intrahospital deaths in 2005 and 2018. Standardized rates defined the following 4 ranges: <25%, 25%–49.9%, 50%–75%, and >75%. CW indicates Central West; N, North; NE, Northeast; S, South; SE, Southeast.

Table 4

Distribution of HCC hospitalization and lethality rates in 2005 and 2018 according to urban and rural demographic data.

	2005				2018					
Municipalities	Hospitalization rate (per 105)	Population	Adjusted Hospitalization Rate (per 105)	Lethality (%)	Hospitalization rate (per 105)	Population	Adjusted Hospitalization Rate (per 105)	Lethality (%)	Changes in adjusted hospitalization rates (%)	Changes in lethality (%)
Integrated into MR (urban)	1.9	91,248,203	2.5	21	4.3	104,009,461	6.0	25	140	19
Small-sized	1.7	4,542,857	2.3	19	3.9	5,109,837	5.5	29	139	52
Medium-sized	1.3	9,013,588	1.7	12	3.8	10,881,526	5.4	26	218	116
Large-sized	1.9	77,691,758	2.6	22	4.4	88,018,098	6.1	25	135	14
Not integrated into MR (rural)	1.3	92,934,991	1.7	22	3.7	104,485,439	5.2	25	206	14
Small-sized	1.1	46,661,002	1.5	18	3.1	50,977,162	4.4	22	193	22
Medium-sized	1.0	22,965,072	1.3	25	3.4	26,236,447	4.8	25	269	1
Large-sized	2.0	23,308,917	2.6	25	5.0	27,271,830	7.0	30	169	20

MR = metropolitan region.

we investigated the longest period of time available, maintaining data consistency. The estimated rates obtained with this study identified temporal changes and geographic differences in HCC distribution for the first time, which might prove useful for a better understanding of the epidemiology of HCC in the country. Hopefully, these results will become useful in terms of future health care policies in the distinct levels of the public administration, including municipal, estate, regional, and national contexts.

Although the findings of this study provide insights into HCC time trends and geographic distribution in Brazil for the first time, the limitations of this study need to be addressed. First, despite the large amount of data covering the entire country, the database does not contain information on comorbidities, therapy, or disease details such as specific histologic features. The retrospective nature of this study restrains the analysis exclusively to the information recorded in the electronic database. Hence, it is possible that relevant variables might not have been contemplated in the study. In addition, repeated hospitalizations cannot be ruled out with the retrospective analysis of the database. Such bias, on the other hand, could be, at least in part, compensated due to differences in the availability and quality of health care in less developed regions of the country, which may affect the available data, resulting in potential discrepancies. Moreover, analyses based on hospital documentation do not contemplate outpatients who had not been submitted to medical procedures requiring hospitalization. Another controversial issue that may arise from this study refers to the concept of the municipality. In addition to geographic peculiarities and diversity, Brazilian cities show considerable heterogeneity and wide differences in population densities. For instance, cities may present populations ranging from one thousand to 20 million inhabitants and would be regarded as municipalities of the same level in the database. The limitations and the possibility of an ecological fallacy[56] have been largely attenuated in this study due to the simplicity and directness of the data, which were entered into a single electronic database. In addition, the use of municipalities may compensate for potential losses due to underreporting or defects of the registry because the system covers the entire country in its minimal administrative units, containing official data.

5. Conclusions

In conclusion, the hospitalization rates for HCC are rising in Brazil, following global trends of HCC prevalence, particularly in the population above 50 years of age. Higher rates in the South and Southeast regions may reflect the better quality of diagnosis but also the presence of major environmental factors, such as obesity and diabetes. Nonetheless, geographic shifts in the hospitalization rates from the South to the Northeast and from urbanized to rural areas appear to support the idea of continuing dynamic changes within the socio-economic environment. Relatively stable lethality rates and length of hospital stay in the context of a dramatic increase in the hospitalization rates for HCC suggest the effectiveness of decentralization and efforts to improve the quality of public health services during the study period. However, the cost for the effective treatment of HCC, along with the rapidly aging population, suggests that HCC will continue to have important socioeconomic implications for the country in the near future.

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Author contributions

EB participated in the conception and design of the study; the acquisition, analysis, and interpretation of the data; and the drafting of the manuscript. JPLM and RRL participated in the acquisition, analysis, and interpretation of the data and in drafting parts of the manuscript. RMP and HSPS participated in the conception and design of the study, obtained funding, analyzed and interpreted the data, and critically revised the manuscript for important intellectual content. All authors gave final approval of the submitted version of the manuscript.

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