Burden of liver disease in Brazil, 1996–2022: a retrospective descriptive study of the epidemiology and impact on public healthcare

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Summary

Background Liver disease is a major cause of mortality and morbidity worldwide and its epidemiology depends on the genetic background, exposure to risk factors, access to healthcare and other sociodemographic characteristics. Brazil is a large country with diverse multicultural and ethnic heritages and important socioeconomic inequalities. The burden of liver disease in Brazil, its regions and population is unknown.

Methods We retrieved data from the Unified Health System regarding liver diseases and analyzed the mortality and morbidity from 1996 to 2022 by gender, race/ethnicity, age, region and overall. We calculated the age-specific risk of deaths by liver disease, age-standardization of the data, mean hospitalization and liver transplant-associated costs.

Findings Malignant neoplasm of the liver and intrahepatic bile ducts, alcohol-associated liver disease, fibrosis, and cirrhosis of the liver, other diseases of the liver, hepatic failure, chronic viral hepatitis were identified as the major causes of death and morbidity in Brazil in the period analyzed. The epidemiology of these diseases was diverse, with variations according to geographic regions, gender and race/ethnicity. The major economic burden of liver disease is related to liver transplants, a common outcome of the progression of these diseases.

Interpretation Liver disease in Brazil is a serious issue for the public health system due to the high number of deaths and increasing mortality rate. Our study contributes as a necessary prerequisite for the development of tailored public health policies aimed at mitigating the increasing burden of liver diseases in specific populations and regions.

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Keywords: Liver disease; Liver transplant; Public health; Burden of disease; Brazil

Introduction

Liver diseases are a serious and growing health issue worldwide, now the 11th leading cause of mortality and also a major cause of morbidity in the population. It is estimated that approximately 2 million deaths per year can be attributed to liver diseases, accounting for 4% of all deaths globally (or 1 out of 25 deaths).[1–3]

Various conditions can lead to liver disease; however, chronic viral hepatitis, alcohol-associated liver disease, metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH) are the leading causes of cirrhosis and liver cancer.[4] All of these conditions impose a significant burden on healthcare systems, as they result in increased hospitalizations, diagnosis tests and exams, medications, and long-term clinical management, including transplantation.[1] In this context, chronic viral hepatitis B and C infections are one of the leading causes of end-stage liver disease and liver transplantation globally.[5] In addition, MASLD/MASH are

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Research in context

Evidence before this study

We searched PubMed and Google Scholar for studies reporting the burden of liver diseases in the world and different countries between July 2022 and July 2023. We used the terms "burden of liver disease" OR "liver disease in Brazil" OR "liver disease in Latin America" OR "liver disease statistics". The studies pointed out that liver disease is a major cause of mortality and morbidity worldwide. Approximately 2 million deaths per year can be attributed to liver diseases in the world (4% of all deaths in a year). Although there is an increasing trend in the mortality rate related to liver disease, specific diseases may vary depending on the country and various sociodemographic factors. Most of the available data on the burden of liver disease is from high-income countries. Data from low- and middle-income countries, including Brazil, are often limited or even neglected.

Added value of this study

To our knowledge, no other studies have investigated the burden of liver disease in Brazil covering national, regional and sociodemographic datasets. Here, we identify the major causes of mortality by liver disease, which resulted in 18–20 deaths per 100,000 inhabitants. This represents 3% of all deaths in the country in 2020 (1 out of 33 Brazilians). We also show that the epidemiology and impact of these diseases on the public healthcare system was distinct depending on the region, gender, age and race/ethnicity. However, data on indigenous peoples (native-Brazilians population) is limited in the datasets.

Implications of all the available evidence

Liver diseases account for a substantial burden of mortality, hospitalization, transplantation, and associated costs in Brazil. This study provides compelling evidence indicating that these diseases are on the rise in the country and can offer guidance in the development of tailored public health policies and evidence-based interventions aimed at mitigating the increasing burden of liver diseases. Combined, the available evidence is a call to action. Liver diseases must be discussed from a global perspective, but the formulation of public health policies must take into account national and subnational factors, as well as specificities from different social groups.

becoming increasingly prevalent, particularly in developed countries, due to the rise in obesity, type 2 diabetes and metabolic syndrome[6–8] and are the fastest growing indication for liver transplantation.[9] In this scenario and with the advent of efficient antivirals, it is expected that metabolic liver diseases will surpass viral hepatitis as the leading cause of end-stage liver disease.[10,11] However, the burden of liver diseases in low- and middle-income countries is not very well described although the prevalence of liver diseases in Latin America and the Caribbean is known to have increased in the last 20 years.[12]

This region comprises countries in Central America, South America, North America (Mexico) and the Caribbean with a population of over 660 million people as of 2023. Within this region, Brazil is not only the largest country by land area, but also has the largest population (207,750,291 people as of 2022) with diverse regional, social, and economic backgrounds. The country has a universal, free public health care system, the *Sistema Único de Saúde* (SUS, or Unified Health System) that registers and reports data from its patients, offering the possibility to analyze the impact of diseases—including liver diseases–within the country. In this study, we evaluated the burden of liver disease in Brazil using the data of the Department of Health Informatics of SUS (DATASUS) from 1996 to 2022. We provide a detailed analyses of the available data in order to contribute to the proposal and implementation of public health policies and research activities in the country.

Methods

Study design and data collection

The data used in this study was obtained from the Hospital Information System of the Unified Health System (SIH/SUS), managed by the Brazilian Ministry of Health, through the Department of Health Care, together with the State Health Departments and Municipal Health Departments. All liver diseases classified by the International Classification of Diseases (ICD10) were analyzed and are described in Supplementary Table S1. The variables and parameters analyzed are defined in Supplementary Tables S2 and S3. Data quality of the database is considered high, as previously shown.[13]

The hospital units participating in SUS (public or private under contract) send the information on hospital admissions to the municipal managers or to the state managers. Then, the information is consolidated in DATASUS, by the Department of Health Informatics of SUS, forming a valuable Database that contains data from a large number of hospital admissions carried out in Brazil and that comprises the whole population serviced by SUS (approximately 70% of the total population). Admission information was retrieved from a list of disorders based on ICD10 codes consisting exclusively of liver diseases (Supplementary Table S4) in order to avoid data contamination by other diseases. The relative incidence of these disorders was analyzed from 1998 to 2021, corresponding to all periods available in the system. Importantly, the data is recorded with a unique ICD10 code, which reflects the main cause of

admission. However, we do not have access to the medical records of the patients; therefore, this administrative database does not allow us to track progressive diseases or any individual information of a particular patient. Costs were corrected by the National Extended Consumer Price Index, which is the official measure of inflation used in Brazil, for each year within the analyzed period. The costs of procedures were classified as in the Management System for Procedures, Medications, Orthotics, Prosthetics, and Special Materials of SUS and retrieved from DATASUS.

Mortality data originates from the Mortality Information System, which is managed by the Department of Health Situation Analysis of the Health Surveillance Secretariat, together with the State and Municipal Health Departments. The Health Departments collect all the death certificates from the registry offices and enter the information into the system, which therefore consists of the entire Brazilian population. Importantly, the main cause of death is coded based on the declaration made by the certifying physician, following rules established by the World Health Organization (WHO). Mortality was analyzed from 1996 to 2020, corresponding to all periods in which the diseases were classified according to ICD10 codes.

The regional divisions in Brazil used in this article, are legally valid administrative divisions of the territory, that are proposed by the Brazilian Institute of Geography and Statistics (IBGE) based on a combination of geographical, economic, and demographic factors. In this context, Brazil is divided into five regions: North, Northeast, Midwest, Southeast and South. Data on the population number was obtained from the census or estimates carried out by IBGE throughout the period of analysis and was used to obtain the rates per 100,000 people. For age standardization, we employed the WHO World Standard Population that projects population estimates from 2000 to 2025.[14]

Analysis

Data were analyzed using R (version 4.1.3) and Rstudio (version 2022.02.1 Build 461). The Jointpoint regression model regarding the mortality rate associated with liver diseases over the years was performed using the package "segmented".[15] This analysis takes a general linear model (GLM) and fits it to a new model to consider a piecewise linear relationship. Differences in slope were tested using the Davies test. This allowed us to investigate whether the dynamics of the mortality rate by liver disease was constant or varied over the analyzed period.

To calculate the risk of death and age standardization of the number of deaths by liver disease in the general population as well as in men and women, we stratified the data by sex and age groups according to the Brazilian Ministry of Health classification: 0–4, 5–9, 10–14, 15–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79 and > 80 years old. Then, for each analysis, we modeled the age-specific risk of death by liver disease using the Hamiltonian Markov chain Monte Carlo (MCMC) algorithm. Then the age-specific risk levels were multiplied by the WHO world standard population (2000–2025) sizes[14] to produce the age-standardized rates. Results were reported with 95% confidence intervals. These steps were performed using the package "surveil".

Data visualization was carried out using ggplot2 and geobr packages.

Role of the funding source

This study was funded by Brazilian funding agencies: CNPq (project #406792/2022-4 and scholarship program), CAPES and FAPEMIG. The funding sources had no involvement in the collection, analysis, and interpretation of the data, writing of the manuscript, or in the decision to submit the paper for publication.

Results

Mortality and morbidity due to liver disease in Brazil by region, types of liver disease, gender, and race and ethinicity

We evaluated the burden of liver disease in Brazil, from 1996 to 2021 using the DATASUS data. We found that deaths from liver disease reached their peak in 2012 (approximately 20.1 deaths per 100,000 people) and has maintained that level since then (Fig. 1a). The standardized number of deaths changed only slightly from 2000 to 2020, with the number of deaths ranging from approximately 21 to 17 deaths per 100,000 people throughout this period (Fig. 1a, insert). Interestingly, the age-specific risk of death from liver disease increases with age (Supplementary Figure S1). We observed that liver diseases have been increasing since 1996 in the Midwest, North, and Northeast regions, while in the Southeast and South regions, the number of deaths remained stable, yet high (Fig. 1b-**c**). Additionally, we found that the mortality rate not only increased since 1998 (11.73%), but had risen alarmingly to 19.03% in 2021 (Fig. 1d). When the data by regions was analyzed we found that the mortality rate was increasing in all regions of Brazil, reaching similar high levels by 2021 (Fig. 1e-**f**). Thus we investigated the causes of death by liver disease in Brazil in the last two decades and further explored the six most common causes of death. According to the ICD10, codes, the classification of the six most common causes of death by liver disease in Brazil were C22: Malignant neoplasm of liver and intrahepatic bile ducts; K70: Alcoholic liver disease; K74: Fibrosis and cirrhosis of liver; K76: Other diseases of liver; K72: Hepatic failure, not elsewhere classified; B18: Chronic viral hepatitis. Alcoholic liver disease (K70) and Malignant neoplasm of liver and intrahepatic bile ducts (C22) deaths have been increasing since 1996, while Fibrosis and cirrhosis of liver (K74) deaths were maintained at

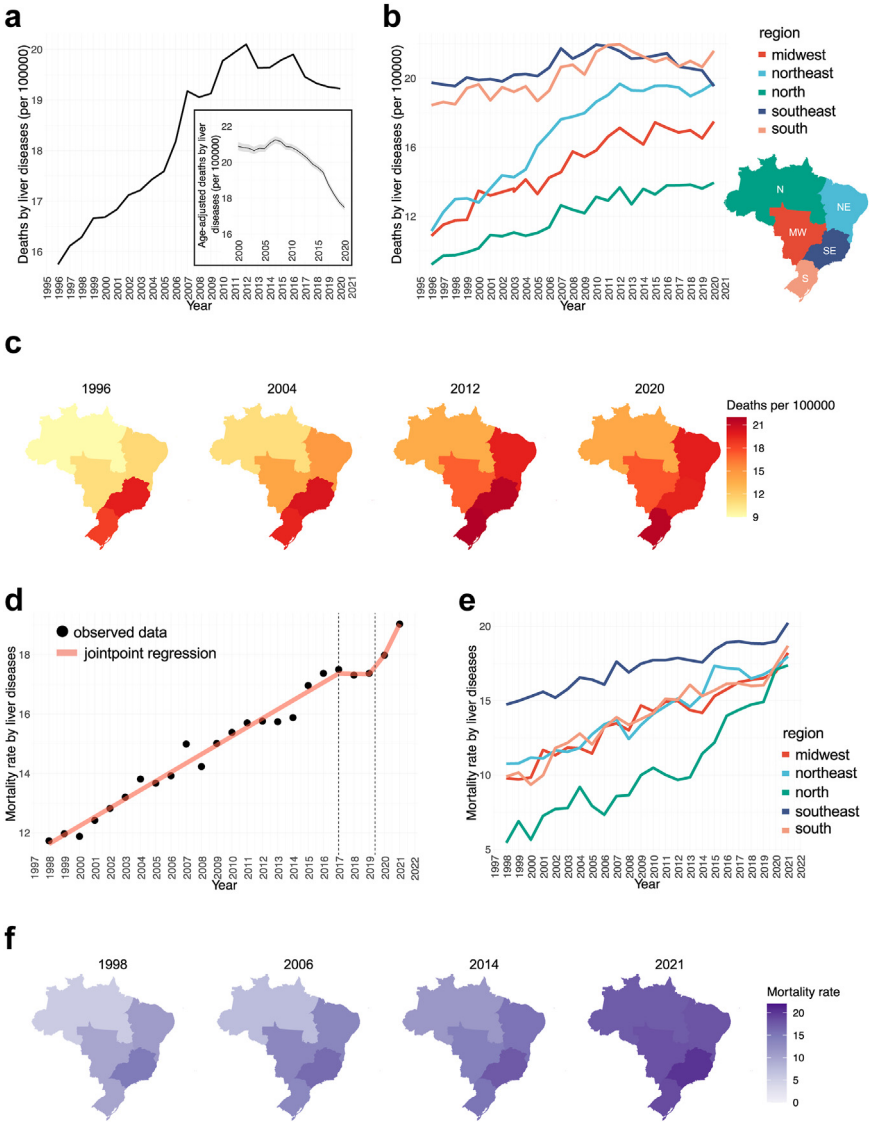

Fig. 1: **Deaths by liver diseases is increasing in Brazil. (a)** Number of deaths by liver diseases per 100,000 from 1996 to 2020. The absolute number of deaths were acquired per year using data from DATASUS of the Brazilian government. It shows a very sharp increase in deaths throughout the first decade, followed by a sustained death number up to 2020, the last year of collected data. Insert: Age standardized number of deaths by liver diseases per 100,000 people. Note that number of deaths is constantly high, with rates comparable to the crude data. Results are expressed as the mean of the respective marginal probability distributions (lines) and the bounds of their central 95% quantile intervals (shaded area). **(b)** Deaths by liver diseases per 100,000 according to geographic regions from Brazil (Midwest, Northeast, North, Southeast, South). Number of deaths has been increasing since 1996 in Midwest, North and Northeast regions and shows a continuous increase in Southeast and South regions, the two most populated regions in Brazil. **(c)** Comparison of the number of deaths in the five regions of Brazil. The maps show data of the number of deaths in approximately every eight years, with deaths per 100,000 people indicated by the color scale on the right side of the panel. **(d)** Jointpoint regression and observed data of mortality rate by liver diseases from 1998 to 2021. There was a steady increase of the mortality rate up to 2017 and a sharper increase from 2019 to 2021. **(e)** Mortality rate by liver diseases according to geographic regions from Brazil. The data show an increased death rate in all Brazilian geographic regions. **(f)** Comparison of the mortality rate in the five regions of Brazil. The maps show data of the rate of mortality of approximately every eight years, with mortality rate indicated by the color scale on the right side of the panel.

high levels throughout the last two decades (Fig. 2a and b). Analyzing the most common cause of deaths by liver disease, the pattern of C22, K70, K74 represented the top three causes of deaths, however each region displayed a more prominent cause of death in the last analyzed year (2020). In the Midwest and Northeast,

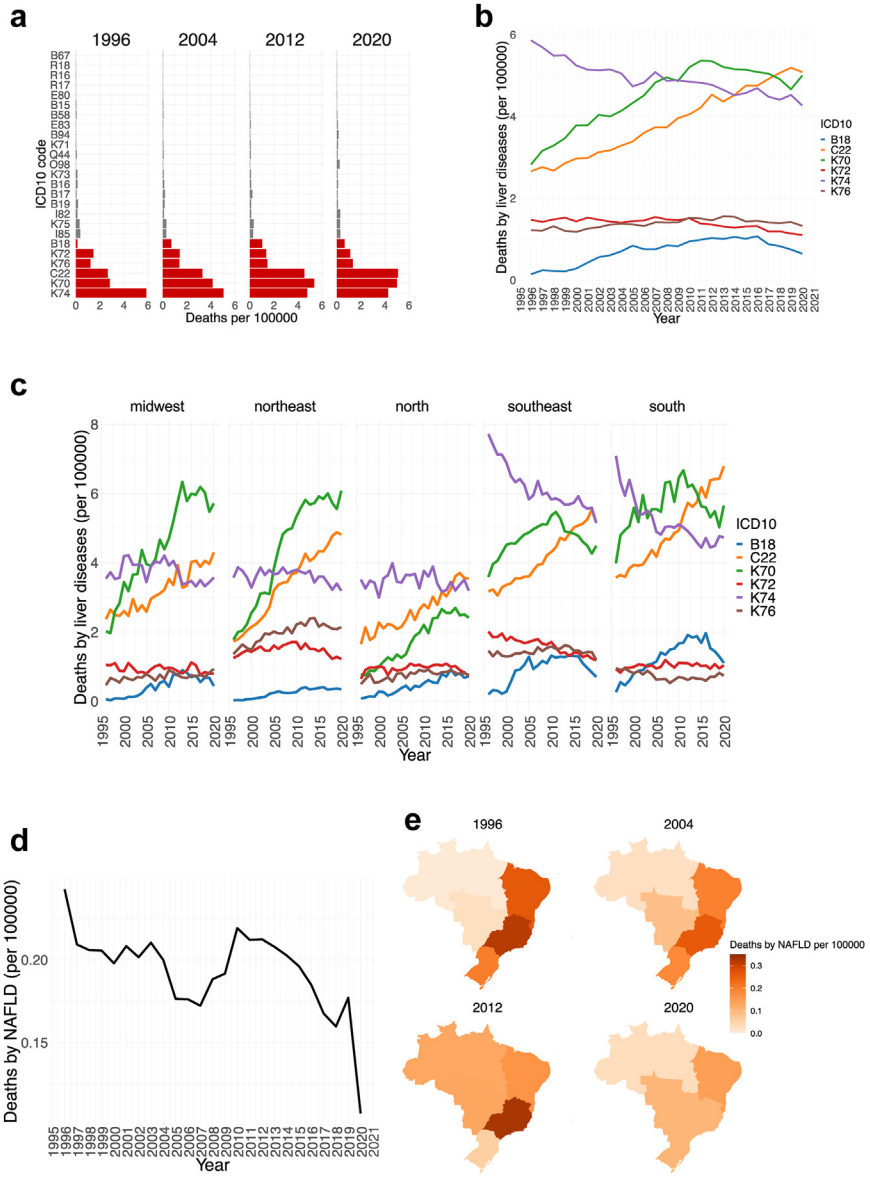

Fig. 2: **Most common cause of death by liver disease in Brazil (1996–2020). (a)** The data was collected from the DATASUS platform and classification made according to the 10th revision of the International of Disease (ICD10). Each code indicates a specific disease, as followed: B67: Echinococcosis; R18: Ascites; R16: Hepatomegaly and splenomegaly, not elsewhere classified; R17: Hyperbilirubinaemia, with or without jaundice, not elsewhere classified; E80: Disorders of porphyrin and bilirubin metabolism; B15: Acute hepatitis A; B58: Toxoplasmosis; E88: Other metabolic disorders; B94: Sequelae of other and unspecified infectious and parasitic diseases; K71: Toxic liver disease; Q44: Congenital malformations of gallbladder, bile ducts and liver; O98: Maternal infectious and parasitic diseases classifiable elsewhere but complicating pregnancy, childbirth and the puerperium; K73: Chronic hepatitis, not elsewhere classified; B16: Acute hepatitis B; B17: Other acute viral hepatitis; B19: Unspecified viral hepatitis; I82: Other venous embolism and thrombosis; K75: Other inflammatory liver diseases; I85: Oesophageal varices; B18: Chronic viral hepatitis; K72: Hepatic failure, not elsewhere classified; K76: Other diseases of liver; C22: Malignant neoplasm of liver and intrahepatic bile ducts; K70: Alcoholic liver disease; K74: Fibrosis and cirrhosis of). The most common deaths by liver disease in Brazil were B18, K72, C22, K70, K74. The graphs show their relation every eight years. **(b)** Timeline of the six most common deaths by liver disease per 100,000 people from 1996 to 2020. Liver cancer (C22) and alcoholic liver disease (K70) have become the most common cause of death by liver disease. Liver fibrosis (K74) is still a concerning cause of death despite the slight reduction of deaths during the past decades. **(c)** Death by the six most common liver diseases in Brazil per 100,000 people varies according to the geographic region. All regions display a growth in the deaths by liver cancer (C22), being the most common cause of death by liver diseases in Southeast, South and North regions. Death by alcoholic liver disease (K70) is growing in the Midwest, Northeast and North regions, being the most prominent cause of death by liver diseases in the midwest and northeast regions. Despite alcohol-associated liver disease and liver fibrosis showing a reduction in the number of deaths and not being the

Alcoholic liver disease (K70) was the main cause of death, while in North and South, Malignant neoplasms of the liver and intrahepatic bile ducts (C22) were the leading diseases. The Southeast region displayed similarly high death rates for both Fibrosis and cirrhosis of liver (K74) and Malignant neoplasm of liver and intrahepatic bile ducts (C22) (Fig. 2c).

Since death by MASLD/MASH is a point of concern worldwide,[6–8] we evaluated deaths due to MASLD and MASH (K75.8; K76.0) in Brazil since 1996 and found a constant trend in Brazil throughout the years (Fig. 2d). By region analysis, both Southeast and Northeast regions displayed the highest number of deaths by MASLD/MASH (Fig. 2e), followed by the South and Midwest regions. Overall, the North region showed the lowest number of deaths from these diseases.

We further examined the age-specific risk of death attributed to liver disease and the age-standardized number of deaths categorized by sex. Notably, men exhibited a consistently elevated risk across all age groups when compared to women (Supplementary Figure S2). Additionally, men recorded a higher overall number of deaths, ranging from 32.5 to 26 per 100,000 people (Supplementary Figure S3). Conversely, women recorded a lower number of deaths due to liver disease, varying between 11.5 and 10.0 deaths per 100,000 people (Supplementary Figure S3). Regarding the prevalence of the six most common causes of death from liver diseases between men and women, we found that overall, men were more susceptible to death by liver disease than women. The three major causes of death by liver disease in men were: Malignant neoplasm of liver and intrahepatic bile ducts (C22), Alcoholic liver disease (K70) and Fibrosis and cirrhosis of liver (K74), while Malignant neoplasm of liver and intrahepatic bile ducts (C22) and Fibrosis and cirrhosis of liver (K74) were the two main causes of death in women in the last two decades (Fig. 3a). Men were at a higher risk of dying from MASLD/MASH than women (Fig. 3b).

Brazil is a diverse country with a complex history of race and ethnicity relations. The population is composed of people of various racial and ethnic backgrounds, including indigenous peoples (native-Brazilians population), Black, White, and Asian descendents. Therefore, we evaluated death by liver disease among different racial/ethnic groups. Asian and Black populations were more affected by Alcoholic liver disease (K70), although at significantly different levels, with overall death being higher in the Asian population (Fig. 3c). In recent years the White population has been more affected by Malignant neoplasm of liver and intrahepatic bile ducts (C22) (Fig. 3c). Death by liver disease subtypes in Indigenous people was not clear, probably due to the difficulty in healthcare access for these populations (Fig. 3d). Deaths by MASLD/MASH were strikingly high in Black and White populations in comparison to the Indigenous and Asian populations (Fig. 3e).

The impact of liver diseases in terms of cost

The cost of hospitalization due to liver disease in Brazil had been increasing from 1998 to 2014 but since 2017 it has been steadily reducing (Fig. 4a). The absolute number of admissions into public health hospitals did not show any significant change throughout the analyzed years, however the population has grown from 161,790,311 in 1998 to 213,317,639 inhabitants in 2021 (Fig. 4b). Surprisingly, there was a 30% reduction in the number of admissions (per 100,000 people) from liver diseases, which contrasted with the increased numbers of deaths and mortality rate in the same period (Fig. 1a–d). The southern regions of Brazil historically displayed the highest mean cost of hospitalization, followed by Northeast and Midwest regions. Importantly, the mean cost of hospitalization for the North region remained at low levels during the last two decades (Fig. 4c). The average length of stay in hospital due to liver diseases did not vary significantly throughout the years evaluated (Fig. 4d).

Next, we investigated the expenses of the national healthcare system on procedures exclusively related to liver diseases in 2021. In this regard, we observed that the highest expenditure was associated with the group of procedures related to liver transplant (68% of total), followed by clinical (25% of total) and surgical procedures (5.8% of total) (Supplementary Figure S4a). Within each group, we noted that liver transplantation with deceased donors accounted for the highest expenditure, followed by the treatment of liver diseases and transplantation with living donors and some surgical procedures, including chemoembolization of liver carcinoma and partial hepatectomy in oncology (Supplementary Figure S4b).

Liver transplant profile in Brazil: numbers and cost

As liver transplant represents the highest expenditure to the Brazilian Unified Health System and is a common outcome of untreated liver disease, we decided to analyze the profile of liver transplant in the last two decades. The number of transplants increased throughout the years mainly due to the use of deceased donors, while living donor transplants remained at low levels and constant throughout the analyzed years (Fig. 5a). Intercurrences related to liver transplant were also analyzed for the last ten years to illustrate additional

major cause of deaths (in 2020) for the Southeast and South regions, these diseases are still a concern due to the high number of deaths in the last decades. **(d)** Deaths by MASLD/MASH per 100,000 people in Brazil. **(e)** Comparison of the number of deaths by MASLD/MASH per 100,000 people in the five regions of Brazil. The maps show data of the number of deaths by MASLD/MASH in every eight years, with the number of deaths indicated by the color scale on the right side of the panel.

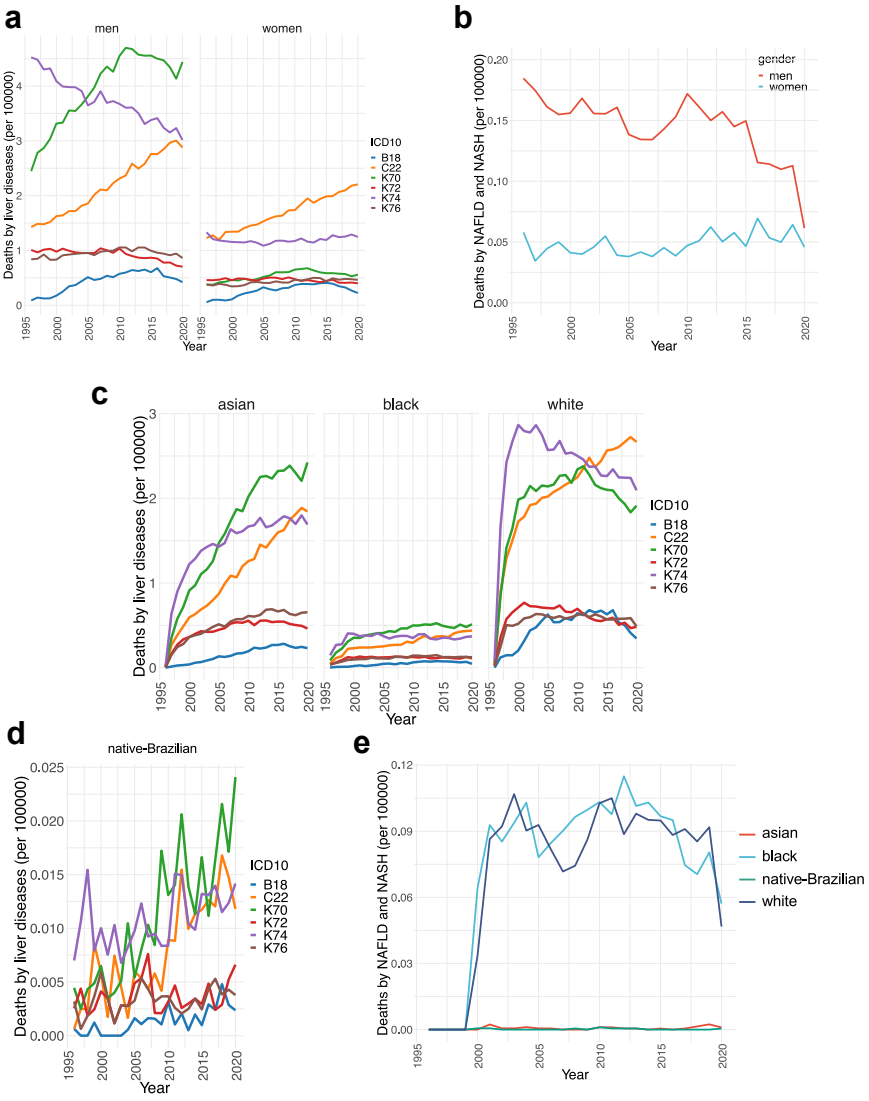

Fig. 3: **Liver disease profile according to gender and ethnic group. (a)** Profile of deaths by liver disease per 100,000 people in Brazil by gender. Men have been more stricken by alcohol-associated liver disease while women more by liver cancer. **(b)** Profile of deaths by MASLD/MASH per 100,000 people in men and women. Men have been more affected than women. **(c)** Profile of deaths by liver disease per 100,000 people in Brazil by ethnic group. Different ethnic groups in Brazil display different liver disease profiles. Asian and Black populations, in the last fifteen years, have been more affected by alcohol-associated liver disease, while the White population, in the last five years, has been more affected by liver cancer. **(d)** Profile of deaths by liver disease per 100,000 people in Native-Brazilian population. **(e)** Deaths by NAFLD per 100,000 people in Brazil according to ethnic group. Black and White populations are significantly more affected by NAFLD than Asian and native-Brazilian populations.

procedures related to liver transplant (Fig. 5b). In the last 10 years, the total cost of liver transplant in Brazil exceeded BRL 200 million (40 milion in USD as of 03/14/2024, or 0.15% of allocated fund for health in 2022; Fig. 5c). We found that the Southern region displayed the highest number of transplants reaching 1.8 transplants per 100,000 people during its peak. In contrast, the Northern region displayed concerningly low numbers of liver transplant throughout the analyzed period with less than 0.2 transplants per 100,000 people (Fig. 5d). The average length of stay in hospital due to both liver transplant and intercurrences showed a big variation among regions during the late 1990s but started to converge to similar numbers during the 2020s.

Discussion

The Brazilian Department of Health Informatics of SUS (DATASUS) was created in 1991 through Decree number 100 of that year. Among its main objectives

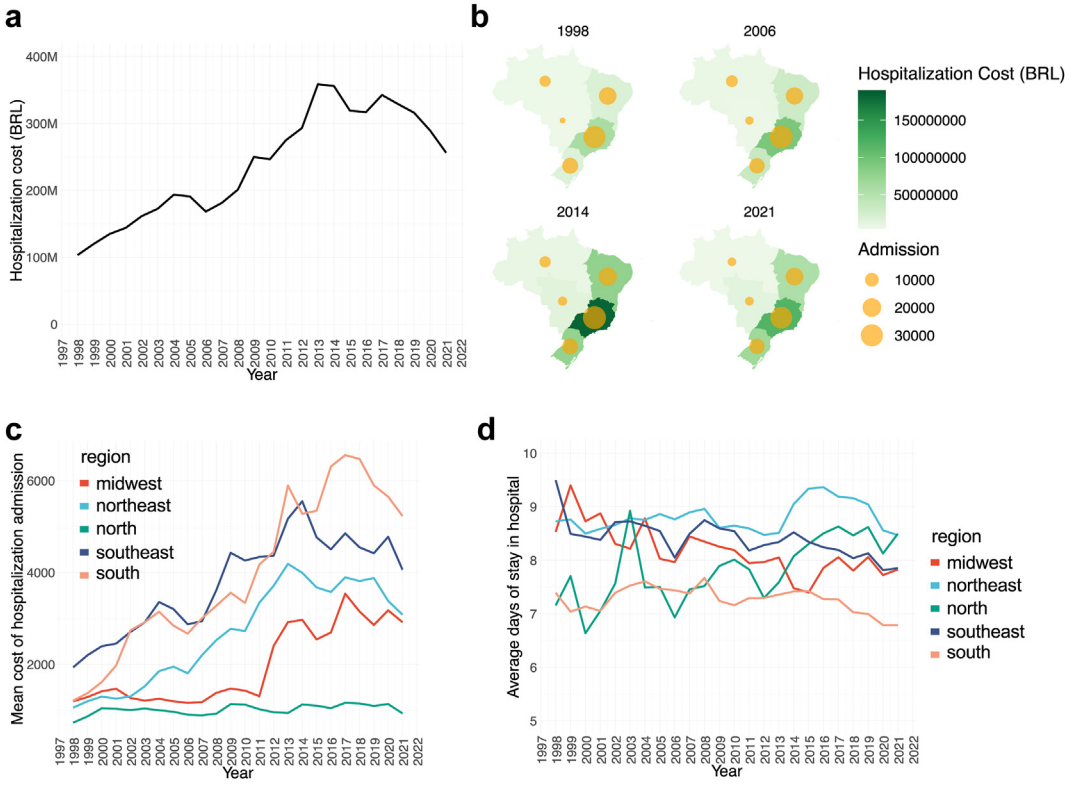

Fig. 4: **Hospitalization cost (BRL) and admission number due to liver disease in Brazil. (a)** Annual cost of hospitalization by liver disease (BRL) from 1998 to 2021. The values of each year were corrected according to the Extended National Consumer Price Index (*Índice Nacional de Preços ao Consumidor Amplo*, calculated by the Brazilian Institute of Geography and Statistics–IBGE). The national annual expense has always been above a hundred million (BRL), reaching as high as three hundred and fifty million (BRL) in the early years of the last decade. **(b)** Geographic representation of hospitalization cost and number of admissions due to liver disease in the indicated years. With the exception of the Northern region, all other regions display an increased hospitalization cost when comparing 1998 to 2021, while the number of admissions due to liver disease remains constant in most regions. **(c)** Mean cost of hospitalization admission (BRL) according to geographic regions. The mean cost of hospitalization admissions has been growing in most regions, while the North region displays a concerningly low uniform cost of its hospitalizations throughout the years. **(d)** Average length of hospitalization stay according to geographic regions. All regions display a similar length of hospitalization, ranging from seven to nine days in hospital.

were the standardized acquisition, processing, and transmission of health information within the scope of the Unified Health System (SUS). This allows for strategic public health management in Brazil and the development of an accurate database associated with mortality and morbidity of diseases with a great geographic and sociodemographic resolution. This is in contrast to approximately one-third of the countries in the world that have inaccurate or absent data collection.[1] Using this system, we have been able to investigate the burden of liver diseases in Brazil using data collected from the 1990s to the 2020s.

The yearly death number and rate of Liver diseases have been increasing in Brazil from 1996 to 2020, reaching 40,716 deaths, accounting for 3% of all deaths in the country, with a mortality rate of 18% in 2020. These numbers are high, especially when compared to other populations. In Europe, age adjusted deaths by liver disease ranged from 36 to below 10 per 100,000 in 2014 and 2015.[16] In this period, age adjusted death numbers in Brazil were approximately 20 per 100,000; and similar rates were observed in only 5 European countries. Liver disease mortality in Brazil is comparable to the US rates, where 17 deaths per 100,000 were observed in 2021.[3,17] The most common causes of death by liver disease in Brazil throughout this period were: Malignant neoplasm of liver and intrahepatic bile ducts, Alcohol assocated liver disease, Fibrosis and cirrhosis of the liver (ICD10C22, K70, and K74, respectively), similar to the main causes of deaths in Europe and United States.[16,17] Although these diseases have always been the most concerning cause of death from hepatic disease in Brazil, they vary according to geographical, demographic, and social factors.

Brazil is one of the most populous countries in the world, with a population over 200 million people (IBGE), and with the majority of its population living in urban areas. The country is divided into five

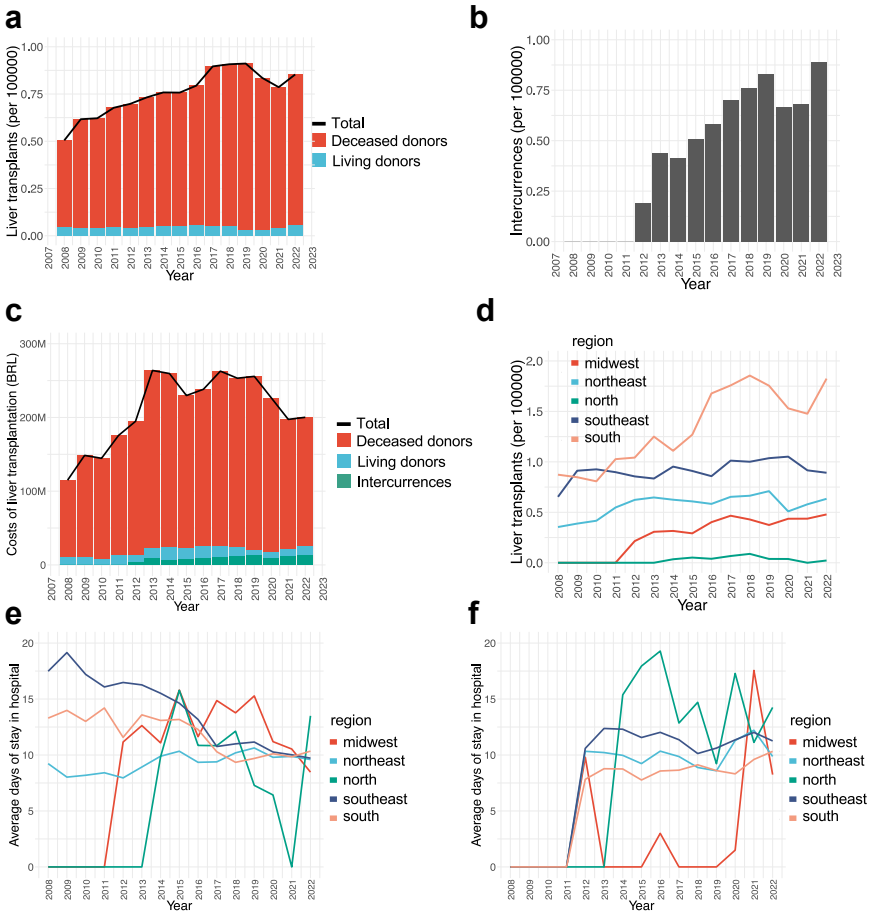

Fig. 5: **Profile of liver transplant in Brazil. (a)** Annual number of liver transplants in Brazil per 100,000 people from 2008 to 2022. The red columns represent the number of transplants from deceased donors, while the blue ones represent the number of transplants from living donors. The black line on top indicates the total number of transplants. **(b)** Number of intercurrences per 100,000 related to liver transplants in Brazil. The number of intercurrences has been growing throughout the years. **(c)** Annual cost of liver transplant (BRL) in Brazil. The red columns represent the liver transplant cost from deceased donors, blue from living donors and green cost from intercurrences related to liver transplants. The black line on top indicates the total cost. **(d)** Number of liver transplants per 100,000 people according to regions in Brazil. In the last decade: the south region is the one with the highest number of transplants per capita followed by the Southeast, Northeast and Midwest regions. The North displays a low number of transplants per capita throughout the years. **(e)** Average days of stay in hospital due to liver transplant according to region. In the years with transplant varies from approximately nine to twenty days of hospitalization. **(f)** Average days of hospitalization due to intercurrence from liver transplants according to the region. In the years that present intercurrences, the average days of stay in hospital varies from, approximately, three to twenty.

geographical regions (North, Northeast, Midwest, Southeast, and South), in which there are significant variations with the more densely populated areas located in the Southeast and coastal regions. In contrast, the North region has the lowest population density. Another point of interest is the socioeconomic inequality observed between the regions of Brazil, as southern regions have higher Human Development Indexes and better access to education, basic services and healthcare than the northern regions.[18]

Malignant neoplasm of liver and intrahepatic bile ducts (C22) have become a major cause of death from liver diseases in Brazil. However, different from K74 and K72, deaths from C22 have been increasing in all regions. Among the diseases classified into the C22 category according to the ICD10 codes, liver cell carcinoma (Hepatocellular carcinoma–HCC) is a major concern for public health. It is well known that HCC is more frequent in males than females and the male:female ratios average from 2:1 to 4:1 in some populations.[19] Considering the number of deaths between men and women, this ratio increased in Brazil from 1997 to 2021, with an average of 2:1 deaths in 2021 attributed to C22. This may relate to a sex-dependent difference in exposure to environmental risk factors, such as alcohol consumption and viral hepatitis. We also

observed that C22 deaths increased in all race/ethnicities analyzed, despite the clear underrepresentation in Black patients. In this regard, the lower number of deaths from liver diseases observed in Black individuals may be indicative of the impact of racial disparities that lead to delayed diagnosis, inequitable access to treatment, and transplantation as already reported in other populations.[20] The lack of data for our Indigenous populations is alarming and there is an urgent need to know the burden of hepatic neoplasms better in this group. This need is supported by the observation that the highest surge in hepatocellular carcinoma (HCC) incidence in the United States was observed in native-American populations.[21]

Alcohol associated liver disease (K70) is another major burden for public health in Brazil. In 2010, alcohol consumption in Brazil averaged 8.5 L similar to the average of the Americas (8.0 L) but higher than the world average (6.4 L). In 2016, alcohol consumption decreased to 7.4 L per capita, however, the proportion of abusive alcohol consumption by Brazilians increased from 12.7% to 19.4% in the same period, contrasting with the global results where this proportion decreased from 20.5% to 18.2%.[22] Interestingly, alcohol abuse has significant regional variations in Brazil, with the Midwest and Northeast regions with the highest proportion of abusive drinking (21.1% and 18.9%, respectively, in 2021).[22] This regional characteristic corroborates our findings that alcoholic-associated liver disease (K70) is the main cause of death by liver diseases in both regions, and which is rapidly increasing. Furthermore, the abuse of alcohol was considerably higher in men (27%) than in women (12.7%) nationwide,[22] which may account for the drastic difference in the number of deaths due to alcohol-associated liver disease between both sexes.

MASLD/MASH is one of the most prevalent liver diseases worldwide, affecting 25% of the population. In Brazil, it is estimated that 35.2% of the population is diagnosed with MASLD, a frequency higher than observed worldwide and in South America (31%).[23] To date, there is no specific classification for these diseases in the ICID10; however, this diagnosis is often recorded by the codes K75.8, K76.0.[24] We observed that the number of deaths attributed to MASLD/MASH in Brazil is stable over the period, but higher in men when compared to women and similar between Whites and Blacks, although it is low in Asian and Indigenous populations. Interestingly, we observed significant regional differences, as the Southeast and Northeast of Brazil showed the highest number of deaths, the South was in the middle while the North had the lowest numbers. In all Brazilian regions, with the exception of the North, the most important dietary items include foods of typical Brazilian diet, such as rice, beans, flours (wheat, manioc, and cornmeal), sugar, butter, margarine, oils, fats, breads, cakes, cookies, and sweetened beverages.[25] These items can be classified as high energy diets. In contrast, the North has the highest consumption of fish, coconut, leafy vegetables, potatoes, others tuberous roots, and fruits,[25] a pattern associated with a healthier diet. Our findings are in line with previous studies showing that Western dietary patterns are associated with higher risk of MASLD. On the other hand, the Prudent or Mediterranean dietary patterns, which are similar in composition to the North region diet, are releated to a decreased risk of the disease.[26] In addition, in Brazil, there is a strong association between dietary patterns and sociodemographic characteristics, including educational level, income, age, sex, and skin color.[27] In the context of the Americas, Brazil has a high prevalence of chronic liver disease due to MALSD (>16,000 per 100,000 inhabitants) in despite of a high variety of publich health policies on MASLD related conditions.[28] However, the lack of MASLD specific public health policies in the country[28] is of concern and may contribute significantly to this scenario. The present findings highlight the importance of such specific policies that should also take into consideration regional characteristics. Additionally, the lack of a specific classification for MASLD and MASH in the ICD10 codes is an important limitation to a complete interpretation of the burden of these diseases in Brazil using an administrative databank as the source of information.

Of the six main causes of deaths by liver diseases in Brazil since 1996, four of them are the major indications for liver transplantation in the country. Together, viral hepatitis (35%), alcohol-associated liver disease and cirrhosis (11%), hepatocellular carcinoma (10%), and cryptogenic or metabolic dysfunction-associated steatohepatitis (10%), account for 66% of liver transplants in the country.[29] The diagnoses of many liver diseases are difficult and their treatments are limited[30]; therefore, it is not surprising that the main economic burden for the Brazilian Unified Health System associated with liver diseases is liver transplantation. Brazil is the third most active country in liver transplantation in the world and the first in Latin America, with approximately 0.9 transplants per 100,000 people. However, this procedure is only available in 14 of the 26 Brazilian states, with most transplant centers concentrated in Southern states.[10] The patients are listed in regional waiting lists and each state that has a transplant center has its own waiting list.[10] Together, these characteristics may explain the discrepancy in the numbers of liver transplants between the regions.

Strengthens and limitations

Our study uses a national administrative dataset to understand the evolution and burden of liver disease in the Brazilian population and subpopulations (regions, gender, race/ethnic and age). By using this strategy, we have access to high quality data of the public health system, which is the primary healthcare provider for

approximately 70% of the population; therefore, increasing the number of observations and geographic coverage of the data. For mortality, the coverage is 100%. However this study has limitations. First, we used the ICD10 to collect the data for the analyses, which lacks a specific classification for MASLD–a disease with a high prevalence within the population. Second, the dataset does not record information about single patients, as the medical record is maintained by each health center. This constraint impossibilitates the calculation of important parameters when studying the burden of disease, such as DALYs. Furthermore, it makes impossible the investigation of progressive diseases, a characteristic of many liver diseases. Additionally, the mortality and morbidity data is recorded with different levels of ICD10 classification (Supplementary Tables S3 and S4), which limits the comparision between both sets.

Conclusion

Liver diseases account for a substantial burden of mortality, hospitalization, transplantation, and associated costs in Brazil. This study provides compelling evidence indicating that these diseases are on the rise in the country, exhibiting distinct regional and sociodemographic patterns. Additionally, this study can offer guidance in the development of tailored public health policies aimed at mitigating the increasing burden of liver diseases.

Contributors

AGO conceived the idea of the analysis, with input of all authors. JSFG, JAM, TYK collected and analyzed all the data in this study, with input from ALMO, MFL, and AGO. JSF, MFL, and AGO interpreted the results with contributions from all authors. ALMO conducted the corrections of costs based on the national extended consumer price index throughout the years. JSFG and AGO have directly accessed and verified the data. JSFG, MFL, and AGO produced the submitted version of the manuscript, with significant contributions from all authors.

Data sharing statement

The findings of this study are supported by data available at public online repositories maintained by the Brazilian Federal government. The system allows anyone who wishes to access the data for any purpose (https://datasus.saude.gov.br/informacoes-de-saude-tabnet/). Data can be retrieved as follows: Morbidity (http://tabnet.datasus.gov.br/cgi/deftohtm.exe?sih/cnv/niuf.def), Procedures (http://sigtap.datasus.gov.br/tabela-unificada/app/sec/inicio.jsp and http://tabnet.datasus.gov.br/cgi/deftohtm.exe?sih/cnv/qiuf.def), Mortality (http://tabnet.datasus.gov.br/cgi/deftohtm.exe?sim/cnv/obt10uf.def).

Editor note

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Declaration of interests

Authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2024.100731.

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