

GLOBAL HEPATOLOGY

Burden of liver disease in Brazil

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Abstract

Background & Aims: The burden of liver diseases in the Brazilian population is still unknown. To assess the impact of liver diseases on hospital admissions and mortality within the framework of the Brazilian Unified Health System. **Methods:** An analytical ecological observational study was carried out. Secondary data on hospital admissions and deaths because of liver disease were collected from the Unified Health System Information Technology Department (DATASUS) database, between 2001 and 2010. All liver diseases included in the International Classification of Diseases (ICD-10) were reviewed. **Results:** Liver diseases were the eighth leading cause of death in Brazil. The prevalence of hospital admission because of liver disease during the period of analysis was 0.72% (853 571 hospitalizations), and the mortality rate was 3.34% (308 290 deaths). The mean age at hospital admission and death because of liver disease was 48.05 and 58.10 years respectively. Both hospitalization and death because of liver disease were more common among men, and followed an upward trend over the years. Cirrhosis was the main cause of hospital admissions and death by liver disease in Brazil. The South region of the country had the highest hospital admission rates because of liver disease in Brazil, whereas the Southeast region had the highest mortality rate. **Conclusion:** This study provides evidence of the relevance of liver diseases within the framework of the Brazilian Unified Health System, and shows that the burden of these diseases is not only significant but progressive, at least in terms of hospital admissions and mortality rate.

Disease generally has significant negative social implications for affected individuals, their families, society and, in a broader sense, the population as a whole. One of the main negative effects of disease on society is reduced economic productivity (1).

An accurate understanding of the true burden of any given disease is essential for the formulation of public health policies designed to prioritize health interventions and research activities which lead to adequate resource allocation. The burden of a disease is a broad concept that encompasses several aspects of population health: the frequency of the disease, as measured by its incidence and prevalence rates; its effect on longevity, in other words, the number of years of life lost as a result of premature death; its morbidity, defined as a decrease in health status and health quality; and its financial impact, including direct and indirect costs related to individual health (1).

Liver diseases are on the rise. By way of illustration, approximately 170 million people worldwide are

currently infected with HCV (2), alcoholic liver disease is the leading cause of death by liver disease in Europe (3) and nonalcoholic fatty liver disease (NAFLD) is increasingly recognized as a common cause of chronic liver disease (4). The prevalence of HCV cirrhosis and its complications will continue to rise over the next decade, and, according to Davis *et al.* (5), the proportion of patients with HCV cirrhosis will reach 45% by 2030. The increasing incidence of chronic liver disease burdens health systems, decreases quality of life and may even influence the productive life span (6).

In Latin America, a Mexican study by Mendez-Sanchez *et al.* (7) projected that nearly 2 million cases of chronic liver disease are expected to occur by the year 2050, and that alcohol-related liver disease will remain the most important aetiology of chronic liver disease, followed by NAFLD.

Brazil is the largest country in South America, with an estimated population of 190 755 799. Over the last two decades, changes in human behaviour and lifestyle

in the country have resulted in a dramatic increase in the prevalence of obesity. According to the latest census by the Brazilian Institute of Geography and Statistics, 40% of Brazilian adults are overweight and 8.9% of males and 13% of females are obese, which may translate to a higher incidence of NAFLD (8).

Regarding HCV, according to a recent population-based survey (9), the overall prevalence of HCV infection in Brazil is 1.38%. This figure reflects the future impact of the complications associated with the natural history of hepatitis C, since most cases go undiagnosed in Brazil, as in other countries (10).

Even though liver diseases are considered, by many healthcare providers, to be of little relevance, some, such as viral hepatitis and NAFLD, are highly prevalent among the population, and others, such as cirrhosis, hepatocellular carcinoma and fulminant hepatitis, are extremely lethal (1).

As countless liver diseases follow an insidious course, it is common for a long time to elapse between onset of the disease and its detection (latent period). It is estimated that the impact of chronic liver diseases will be even more substantial, partly because of the increasing prevalence of certain such conditions, including cirrhosis and hepatocellular carcinoma secondary to nonalcoholic liver disease and to hepatitis C (5, 11).

The aim of this study was to evaluate the burden of liver diseases in Brazil, within the scope of the Unified Health System, between the years 2001 and 2010.

Methods

An analytical ecological observational study was conducted using the largest public health database available in Brazil, DATASUS. The data contained therein are made available by the Brazilian Ministry of Health through the web portal of the Unified Health System Information Technology Department (www.datasus.gov.br).

The two primary outcomes of this study were the rates of hospital admission and mortality because of liver disease in the 2001–2010 period. All conditions classified as liver diseases in the International Classification of Diseases (ICD-10) were considered for analysis.

The independent variables collected were gender (male/female) and age (in years).

Deaths by liver disease were defined as those in which the death certificate listed a liver disease as the cause of death. For purposes of analysis of the outcome hospital admissions for liver disease, all data from Authorizations for Hospitalization that bore an ICD code for liver disease were also collected. Records with missing data for the period of interest were excluded.

States were defined as the units of analysis because reliable ecological data were available for the proposed period of analysis and because there is lower fluctuation in mortality rates and population size at the state level than at smaller units of analysis. The use of states as the

aggregation level may also mitigate potential contamination effects observed when smaller units of analysis are used to evaluate mortality. The regions of Brazil are legally valid subnational entities proposed by the Brazilian Institute of Geography and Statistics (*Instituto Brasileiro de Geografia e Estatística*, IBGE), and 2010 IBGE census data were used.

Initially, a descriptive analysis of the main causes of mortality in Brazil was carried out. Data on hospital admissions and their main causes were then described. Finally, association tests were conducted to ascertain whether statistically significant differences existed among the independent variables studied and the outcome of interest (hospital admissions). Hospital admission rate data are stratified by region. A similar descriptive and bivariate analysis was carried out for mortality data. For this purpose, data were extracted and analysed using Tabwin software. A total of 2916 files were evaluated (number of states \times number of months in a year \times period of analysis), and each file was run separately.

This study project was approved by the Universidade Federal de Ciências da Saúde de Porto Alegre Research Ethics Committee with judgment number 1430/11. All data were anonymized for analysis, and the project was conducted so as to prevent any identification of patients in disclosures that may result from this study.

Results

Overall countrywide mortality

From 2001 to 2009, 9 237 149 deaths occurred in Brazil. Table 1 describes the 10 leading causes of death, according to DATASUS data, during this study period.

Diseases of the digestive system were the seventh leading cause of death. Considering that liver diseases led to 308 290 deaths during this study period, which corresponds to 68% of deaths from digestive disease, one may infer that liver disease *per se* is the eighth leading cause of death in Brazil, behind infectious and parasitic diseases.

Hospital admissions

Between 2001 and 2010, there were 117 979 343 hospital admissions in Brazil. Of these, 853 571 were because of liver disease, which corresponds to 0.72%.

Of all hospitalizations because of liver disease, 573 293 (67.16%) involved male patients and 280 275 (32.83%) involved female patients ($P < 0.001$). The mean age at hospital admission for liver disease was 48.05 years.

A graphical representation of these values during the 10-year study period is shown in Figure 1.

As the graph shows, the absolute number of hospital admissions because of liver disease in Brazil has been on the rise, especially since 2007 ($P < 0.001$).

Table 1. Distribution of the 10 leading causes of death in Brazil by ICD-10 chapter, 2001–2009

Rank	Chapter	N	%
1	Diseases of the circulatory system	2 623 605	28.40
2	Neoplasms	1 335 400	14.46
3	External causes of morbidity and mortality	1 163 317	12.59
4	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	958 695	10.38
5	Diseases of the respiratory system	909 155	9.84
6	Endocrine, nutritional and metabolic diseases	507 708	5.50
7	Diseases of the digestive system	452 964	4.90
8	Certain infectious and parasitic diseases	416 193	4.51
9	Certain conditions originating in the perinatal period	266 941	2.89
10	Diseases of the genitourinary system	158 835	1.72
Total		8 792 813	95.19

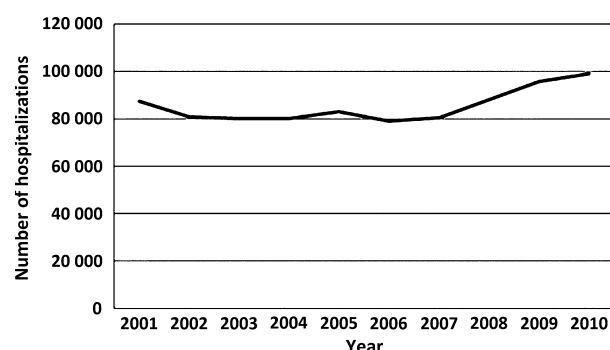
**Fig. 1.** Absolute number of hospitalizations because of liver disease in Brazil, 2001–2010.

Table 2 lists the main causes of hospital admission for liver disease in Brazil during this study period and their respective ICD-10 codes. These 10 causes accounted for approximately 66% of all hospital admissions because of liver disease in the period of interest.

As these data show, over one-third of hospitalizations for liver disease were because of cirrhosis (ICD-10 codes K74.6 and K70.3), with an average rate of 29 800 hospital admissions per year.

Most hospital admissions because of cirrhosis and liver failure in Brazil involved patients between the ages of 40 and 59.

Table 3 shows the absolute number of hospitalizations for liver disease in the five macro-regions of the country during this study period.

Analysis of variance revealed statistically significant differences among regions ($P < 0.001$). The greatest difference was found between the Center-West and South regions of Brazil.

Mortality

Mortality data are presented from 2001 to 2009, as not all data for 2010 were available from the DATASUS portal at the time of writing.

From 2001 to 2009, 9 237 149 deaths occurred in Brazil. Of these, 308 290 were caused by liver disease (3.34%); 220 255 (71.44%) of decedents were male and 87 993 (28.54%) were female ($P < 0.001$). The average age at death because of liver disease during this period was 58.1 years.

A graphical representation of these values is shown in Figure 2.

As Figure 2 shows, liver disease-related mortality has been on an upward trend over the years ($P < 0.001$).

Table 2. Leading causes of hospitalization for liver disease in Brazil, 2001–2010

Rank	Cause	ICD	N	%
1	Other and unspecified cirrhosis of liver	K74.6	196 148	22.98
2	Alcoholic cirrhosis of liver	K70.3	101 859	11.93
3	Acute and subacute hepatic failure	K72.0	73 384	8.59
4	Unspecified viral hepatitis without hepatic coma	B19.9	46 904	5.49
5	Biliary cirrhosis, unspecified	K74.5	42 906	5.02
6	Abscess of liver	K75.0	27 988	3.27
7	Hepatitis A without hepatic coma	B15.9	22 518	2.63
8	Malignant neoplasm of liver, not specified	C22.9	16 994	1.99
9	Alcoholic hepatic failure	K70.4	16 148	1.89
10	Hepatic failure, unspecified	K72.9	15 166	1.77
Total			560 015	65.60

Table 3. Percentage of hospital admissions for liver disease in the five macro-regions of Brazil, 2001–2010

Macro-regions	Total population	% of total admissions
North	15 864 454	0.43
Northeast	53 081 959	0.38
Southeast	80 364 410	0.47
Center-West	14 048 094	0.36
South	27 386 891	0.55

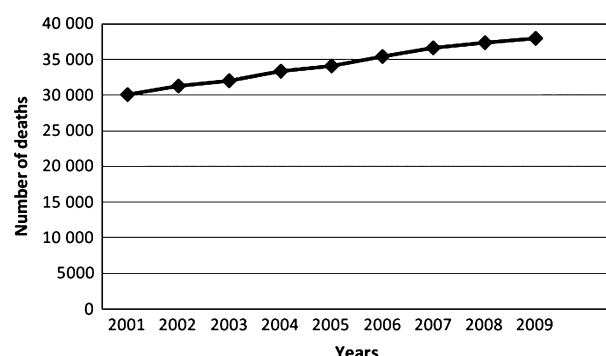
**Fig. 2.** Absolute number of deaths because of liver disease in Brazil, 2001–2009.

Table 4 lists the 10 leading causes of death because of liver disease in Brazil during the 2001–2009 period and their respective ICD-10 codes.

The 10 causes listed above accounted for approximately 80% of deaths because of liver disease in the country during the 2001–2009 period; the three leading conditions (other and unspecified cirrhosis, alcoholic cirrhosis, and malignant neoplasm of the liver, not specified) accounted for more than half of all deaths because of liver disease during this study period.

Cirrhosis (represented by ICD-10 codes K74.6 and K70.3) was the leading cause of liver disease-related mortality in Brazil during this study period, with an average of 14 342 deaths per year, more than half of these occurring in the Southeast region of the country.

Liver disease mortality was most common in the 40-to-79-year age range, and least prevalent in the under-20 age group.

When liver disease mortality rates for this period were disaggregated by macro-region, a distinct distribution was observed (Table 5).

Analysis of variance revealed statistically significant differences ($P < 0.001$). The greatest difference was found between the North and Southeast regions.

Discussion

This study analysed the impact of liver diseases in Brazil in terms of hospital admissions and mortality between the years 2001 and 2010, using information drawn from a nationwide database.

Two limitations inherent to ecological studies must be mentioned: the issue of secondary data, which are subject to registration error; and the ecological fallacy – the extrapolation of population-wide findings to the individual level. Therefore, the results of any ecological study should be interpreted cautiously.

On the other hand, ecological study designs are highly valuable for the generation of hypotheses that may later be confirmed by further research. Even though the results reported herein were derived from secondary data, to the best of our knowledge, this is the first-ever report of this nature in the Brazilian literature. Another positive aspect concerns the database used for this study, DATASUS, which is the largest in the country.

Liver disease-related mortality is increasing worldwide (12). In the UK, liver disease is the fifth leading cause of death, after heart disease, stroke, respiratory disease and cancer (13). In the USA, chronic liver disease and cirrhosis is the twelfth leading cause of death, claiming 30 000 lives annually (14), which is consistent with the projections made by Murray and Lopez using a mathematical model (15). In Asia, as in Brazil, liver diseases were the eighth leading cause of death in 2009 (16).

In Latin America, alcohol consumption (one of the main risk factors for liver disease) far exceeds the world-wide average (17). In Brazil, 54% of the population consumes alcoholic beverages on a regular basis, i.e. at least once a week (18), which may predispose to the development of chronic liver disease. Despite the low estimated prevalence of HCV in Brazil at 1.38% (9), the prevalence of HCV cirrhosis and its complications is expected to continue to rise worldwide (5). Also worthy of note is a recent study (19) that demonstrated an increase in the prevalence of obesity in Brazil in the last few years, which may contribute to an increased incidence of NAFLD and its consequences. Supporting this assertion is a Brazilian study that evaluated the epidemiology and clinical characteristics of NAFLD in 1280 patients and observed obesity in 44.7% and overweight in 44.4% of cases (8). Taking these factors into account, the role of liver disease as a leading cause of death in Brazil is understandable.

From 2001 to 2010, 853 571 hospital admissions attributable to liver disease occurred in Brazil. Cirrhosis, regardless of aetiology, constitutes the leading cause of hospitalization for liver disease in Brazil, accounting for 35% of these hospitalizations at an average rate of 29 800 admissions per year. In the USA, Nguyen *et al.* (20) reported an annual rate of 50 000 admissions because of cirrhosis, and Berman *et al.* (21) found that approximately 20% of patients who survived hospitalization were readmitted within 30 days. Hence, there is a difference in hospitalization rates between Brazil and the USA, possibly because the quality of reporting is superior in the latter country.

Disaggregation of liver disease-related hospital admissions by the five macro-regions of Brazil showed a

Table 4. Leading causes of death because of liver disease in Brazil, 2001–2009

Rank	Cause	ICD	N	%
1	Other and unspecified cirrhosis of liver	K74.6	80 655	26.16
2	Alcoholic cirrhosis of liver	K70.3	48 333	15.68
3	Malignant neoplasm of liver, not specified	C22.9	41 769	13.55
4	Hepatic failure, unspecified	K72.9	20 688	6.71
5	Liver disease, unspecified	K76.9	12 472	4.04
6	Liver cell carcinoma	C22.0	10 791	3.50
7	Alcoholic hepatic failure	K70.4	9644	3.13
8	Chronic viral hepatitis C	B18.2	9111	2.95
9	Alcoholic liver disease, unspecified	K70.9	8756	2.84
10	Acute hepatitis C	B17.1	3853	1.25
Total			246 072	79.81

Table 5. Percentage of deaths by liver disease in the five macro-regions of Brazil, 2001–2009

Macro-regions	Total population	% of total deaths
North	15 864 454	0.09
Northeast	53 081 959	0.14
Southeast	80 364 410	0.18
Center-West	14 048 094	0.12
South	27 386 891	0.17

statistically significant difference between the Center-West region (that with the lowest rates of hospitalization) and the South region (where the highest rates of hospitalization for liver disease are found). This difference is probably because of divergences in the quality of data registries.

With regard to mortality, during this study period, 308 290 deaths because of liver disease were reported in Brazil, and the number of these deaths followed an upward trend over the years.

Cirrhosis, the twelfth leading cause of death in the USA in 2007, has a significant impact on the economy, with a cost burden estimated at 14 million to 2 billion USA dollars as of 2008, depending on the aetiology of the disease. This burden is expected to grow over the course of the next 20 years, as the percentage of patients with HCV-related cirrhosis increases (22). In the present study, cirrhosis was the leading cause not only of hospitalization, but also of mortality because of liver disease in Brazil, accounting for 128 988 deaths in this study period (representing 42% of deaths because of liver diseases and an average of 14 342 deaths a year).

Stratification of liver disease-related mortality rates by region showed a statistically significant difference between the North regions, which had the lowest rates of death and the Southeast region, with the highest. Again, this difference was probably because of the quality of vital records. According to a recently published Brazilian study on the quality of vital registration (essentially, births and deaths), the farther a municipality is from the state capital, the poorer the

quality of records, most likely because of insufficiency of the health services and a lack of skilled professionals to provide timely, adequate care, as well as to a need for adjustments in the consolidation of vital records (23). The North region of Brazil is the least developed and access to accurate information is limited.

Brazil does not have a reliable or easily accessible vital records system. This is a substantial challenge to studies such as this one, and may lead to error. Although the Brazilian Health Information System (*Sistema de Informação em Saúde*, SIS) has been in place for many years, and despite consensus as to its importance as an instrument of health surveillance and management and the high adherence of health services and health professionals to reporting, official estimates state that 17.7% of all deaths occurring annually in the country go unreported. Incompletely filled death certificates are also a problem, especially when data on the basic cause of death are missing (24).

Finally, this study demonstrated the relevance of liver diseases in Brazil, as shown by progressive increases in the rates of hospitalization and mortality attributable to these conditions. As liver disease increasingly becomes a source of negative consequences to individuals and to society, we believe that only the combined efforts of governments (by means of health policies), health agencies and healthcare providers of all levels may stem the rising tide of chronic liver disease worldwide. Prevention and early treatment of these conditions (such as HCV infection, alcoholic liver disease and NAFLD), reducing their comorbidities, the complications associated with cirrhosis and the need for liver transplantation, will also mitigate the economic burden of chronic liver disease.

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References

- Kim WR, Brown RS Jr, Terrault NA, El-Serag H. Burden of liver disease in the United States: summary of a workshop. *Hepatology* 2002; **36**: 227–42.
- Lauer GM, Walker BD. Hepatitis C virus infection. *N Engl J Med* 2001; **345**: 41–52.
- Rehm J, Taylor B, Mohapatra S, et al. Alcohol as a risk factor for liver cirrhosis: a systematic review and meta-analysis. *Drug Alcohol Rev* 2010; **29**: 437–45.
- Clark JM. The epidemiology of nonalcoholic fatty liver disease in adults. *J Clin Gastroenterol* 2006; **40**: S5–10.
- Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. *Gastroenterology* 2010; **138**: 513–21, 21 e1–6.
- Rakoski MO, Mccammon RJ, Piette JD, et al. Burden of cirrhosis on older Americans and their families: analysis of the health and retirement study. *Hepatology* 2012; **55**: 184–91.
- Mendez-Sanchez N, Villa AR, Chavez-Tapia NC, et al. Trends in liver disease prevalence in Mexico from 2005 to 2050 through mortality data. *Ann Hepatol* 2005; **4**: 52–5.
- Cotrim HP, Parise ER, Oliveira CP, et al. Nonalcoholic fatty liver disease in Brazil. Clinical and histological profile. *Ann Hepatol* 2011; **10**: 33–7.
- Pereira LM, Martelli CM, Moreira RC, et al. Prevalence and risk factors of hepatitis C virus infection in Brazil, 2005 through 2009: a cross-sectional study. *BMC Infect Dis* 2013; **13**: 60.
- Jacobson IM, Davis GL, El-Serag H, Negro F, Trepo C. Prevalence and challenges of liver diseases in patients with chronic hepatitis C virus infection. *Clin Gastroenterol Hepatol* 2010; **8**: 924–33; quiz e117.
- Lim YS, Kim WR. The global impact of hepatic fibrosis and end-stage liver disease. *Clin Liver Dis* 2008; **12**: 733–46.
- Simard EP, Ward EM, Siegel R, Jemal A. Cancers with increasing incidence trends in the United States: 1999 through 2008. *CA Cancer J Clin* 2012; **62**: 118–28.
- Bhala N, Aithal G, Ferguson J. How to tackle rising rates of liver disease in the UK. *BMJ* 2013; **346**: f807.
- Asrani SK, Larson JJ, Yawn B, Therneau TM, Kim WR. Underestimation of liver-related mortality in the United States. *Gastroenterology* 2013; **145**: e1–2.
- Murray CJL, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *Lancet* 1997; **349**: 1498–504.
- Korean Statistical Information Service (Kosis). Annual report on the cause of death statistics, 2010. Available at: <http://kosis.kr/eng/>. Accessed 2 August 2012.
- Monteiro MG. Alcohol and public health in Latin America: how to prevent a health disaster? *Adicciones* 2013; **25**: 99–105.
- Laranjeira R, Madruga CS, Pinsky I, et al. *II Levantamento Nacional de Alcool e Drogas - Consumo de Alcool no Brasil: Tendências entre 2006/2012*. São Paulo: INPAD, 2013. Available at: http://inpad.org.br/wp-content/uploads/2013/04/LENAD_PressRelease_Alcohol_RVW.pdf. Accessed 11 March 2013.
- Moura EC, Claro RM. Estimates of obesity trends in Brazil, 2006–2009. *Int J Public Health* 2012; **57**: 127–33.
- Nguyen GC, Segev DL, Thuluvath PJ. Nationwide increase in hospitalizations and hepatitis C among inpatients with cirrhosis and sequelae of portal hypertension. *Clin Gastroenterol Hepatol* 2007; **5**: 1092–9.
- Berman K, Tandra S, Forssell K, et al. Incidence and predictors of 30-day readmission among patients hospitalized for advanced liver disease. *Clin Gastroenterol Hepatol* 2011; **9**: 254–9.
- Neff GW, Duncan CW, Schiff ER. The current economic burden of cirrhosis. *Gastroenterol Hepatol* 2011; **7**: 661–71.
- Rodrigues M, Bonfim C, De Frias PG, et al. Differentials in vital information in the state of Pernambuco, Brazil, 2006–2008. *Rev Bras Epidemiol* 2012; **15**: 275–84.
- Ministério da Saúde, Brazil. *Saúde Brasil 2004: uma análise da situação de saúde*. Brasília: Departamento de Análise de Situação em Saúde, 2004.