

Mortality Associated with Hepatobiliary Disease in Portugal between 2006 and 2012

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Keywords

Hepatobiliary disease · Mortality · Alcoholic liver disease · Hepatocellular carcinoma

Abstract

Introduction: Hepatobiliary disease is becoming a major public health problem, and recent data suggest that the burden of liver disease is higher than previously thought. Our aim was to quantify the mortality from hepatobiliary disease in Portugal and to compare this with the mortality related to other causes over a 7-year period (2006–2012). **Materials and Methods:** A statistical analysis of mortality data according to cause, sex, age, and region from the National Statistics Institute in Portugal was carried out. The data related to 14 causes of death, the most frequent of which were alcoholic liver disease (ALD) (International Classification of Diseases code K70), unspecified cirrhosis of liver (UCL) (K74.6), hepatocellular carcinoma (HCC) (C22.0), unspecified malignant neoplasm of liver (C22.9), and cholangiocarcinoma (C22.1). **Results:** Between 2006 and 2012, 18,279 deaths (24.5/100,000) from hepatobiliary disease were registered in Portugal, constituting the 8th leading cause of death. The main causes of death from hepatobiliary disease were ALD (7.1/100,000), UCL (5.5/100,000), and HCC (4.3/100,000), with a male pre-

dominance (72%). ALD was the main aetiology in younger age groups (40–65 years), while primary neoplasms of the liver and the intrahepatic bile ducts were predominant in the elderly (>80 years). The mortality related to HCC increased by 66% between 2006 and 2012. **Conclusion:** These data outline the burden of hepatobiliary disease in Portugal (8th cause of death) and highlight a potential impact on economic productivity.

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Mortalidade por doença hepatobiliar em Portugal entre 2006 e 2012

Palavras Chave

Doença hepatobiliar · Mortalidade · Doença hepática alcoólica · Carcinoma hepatocelular

Resumo

Introdução: A doença hepatobiliar representa um importante problema para a saúde pública e dados recentes sugerem que o seu impacto é superior ao que se pensava. O

nosso objetivo foi quantificar a mortalidade por doença hepatobiliar em Portugal e compará-la com a mortalidade por outras causas, durante um período de sete anos (2006–2012). **Materiais e Métodos:** Foi feita uma análise estatística da mortalidade por doença hepatobiliar em Portugal, de acordo com a causa de morte, sexo, idade e região geográfica, com dados fornecidos pelo Instituto Nacional de Estatística. Foram estudadas 14 causas de morte, sendo as principais a doença hepática alcoólica (código da Classificação Internacional de Doenças, 10ª versão: K70), cirrose hepática não especificada (K74.6), carcinoma hepatocelular (C22.0), neoplasia maligna do fígado não especificada (C22.9) e colangiocarcinoma (C22.1). **Resultados:** Entre 2006 e 2012 foram registadas 18,279 mortes (24.5/100,000) por doença hepatobiliar em Portugal, sendo a 8ª causa de morte no país. As principais causas de morte por doença hepatobiliar foram a doença hepática alcoólica (7.1/100,000), cirrose hepática não especificada (5.5/100,000) e carcinoma hepatocelular (4.3/100,000), com predominância no sexo masculino (72%). A doença hepática alcoólica foi a principal causa de morte nos grupos etários mais jovens (40–65 anos), enquanto que a neoplasia do fígado e vias biliares intra-hepáticas foi a principal causa nos idosos (>80 anos). A mortalidade por carcinoma hepatocelular aumentou 66% de 2006 a 2012. **Conclusões:** Este estudo salienta o impacto que a doença hepatobiliar tem em Portugal (8ª causa de morte), o que representa um potencial impacto para a produtividade do país.

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Table 1. Reported causes of death from hepatobiliary disease according to the ICD (10th revision)

ICD code(s)	Description
B15–17	acute hepatitis A, B, C, D, E
B18.1	chronic viral hepatitis B without delta agent
B18.2	chronic viral hepatitis C
B18.9	chronic viral hepatitis, unspecified
B19	unspecified viral hepatitis
B19.9	unspecified viral hepatitis without hepatic coma
C22	malignant neoplasm of liver and intrahepatic bile ducts
C22.0	hepatocellular carcinoma
C22.1	cholangiocarcinoma
C22.2	hepatoblastoma
C22.3	angiosarcoma of liver
C22.7	other specified carcinomas of liver
C22.9	unspecified malignant neoplasm of liver
C23	malignant neoplasm of gallbladder
E83.0	Wilson disease
E83.1	haemochromatosis
E88.0	alpha-1-antitrypsin deficiency
K70	alcoholic liver disease
K71	toxic liver disease
K72.1	chronic hepatic failure
K72.9	hepatic failure, unspecified
K74.0	hepatic fibrosis
K74.3	primary biliary cirrhosis
K74.4	secondary biliary cirrhosis
K74.5	biliary cirrhosis, unspecified
K74.6	other and unspecified cirrhosis of liver
K75.4	autoimmune hepatitis

ICD, International Classification of Diseases.

Introduction

Hepatobiliary disease is becoming a major public health problem, and recent data suggest that the burden of liver disease is higher than previously thought [1]. If we aggregate mortality data from chronic liver conditions such as hepatitis C, hepatitis B, and hepatocellular carcinoma (HCC), the burden of liver-related mortality is much higher, with around 2 million deaths occurring each year [2–4]. There is also evidence to suggest that mortality related to liver cirrhosis and liver cancer has increased over the last decade [5]. According to Eurostat figures, liver disease was the 7th leading cause of death in 2013, with noticeably higher rates in certain countries [6]. However, very few studies have analysed mortality related to chronic liver conditions such as liver cirrhosis and

HCC by aggregating data from major causes, namely excessive alcohol intake, hepatitis B and C, and metabolic syndrome [7].

According to the World Health Organization, hepatobiliary disease is one of the top ten causes of death in Portugal [8]. However, data remain insufficient as the burden of liver disease is currently based on information obtained through hospital admissions from liver cirrhosis [9, 10] and HCC [11]. Unlike other countries, aggregated mortality data for hepatobiliary disease in Portugal are yet to be communicated.

One of the main causes of death from hepatobiliary disease is liver cirrhosis due to alcohol consumption. Mortality from liver disease in Europe is closely related to the pattern of alcohol consumption [12], and Portugal is among the 15 countries with the highest alcohol con-

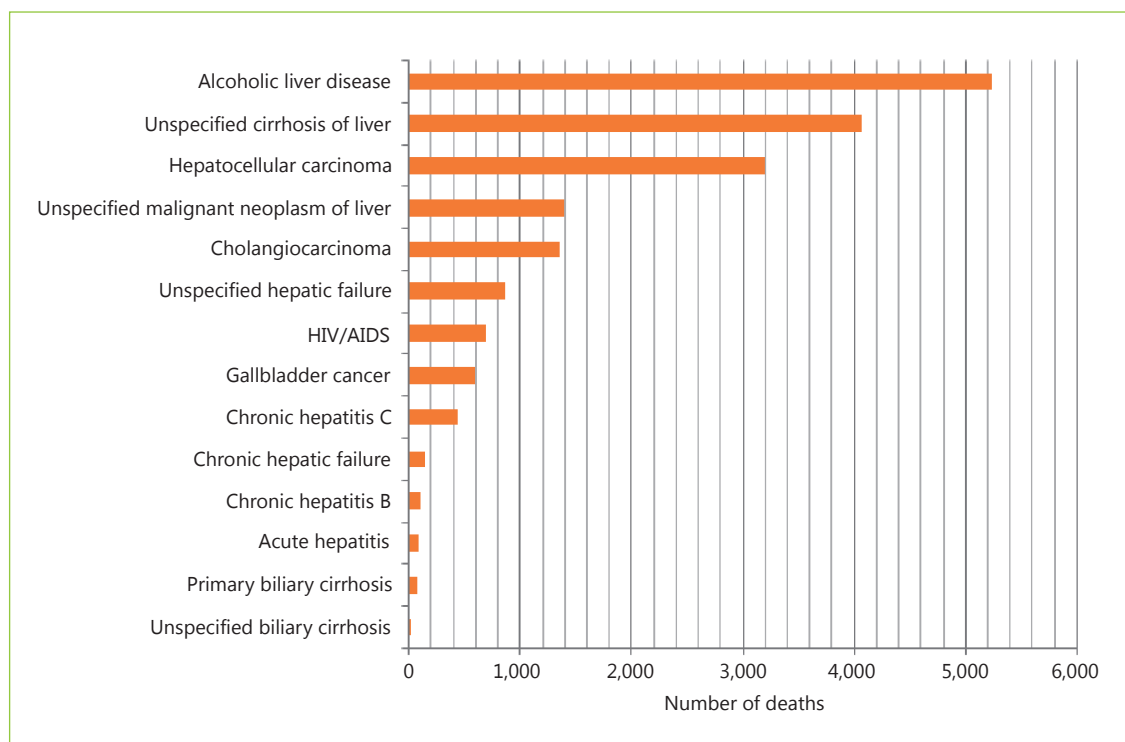


Fig. 1. Number of deaths from hepatobiliary disease in Portugal, 2006–2012. AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus.

sumption per capita in the world [13]. Chronic viral hepatitis is another important cause of hepatobiliary mortality, particularly chronic hepatitis B and C, due to progression to cirrhosis and/or HCC. In Portugal, the prevalence of chronic carriers of hepatitis B virus (HBV) and hepatitis C virus (HCV) is approximately 1% [14, 15]. HCC accounts for approximately 80% of all primary neoplasms of the liver and is the 6th leading cause of cancer death among men [16]. In Portugal, high alcohol consumption and hepatitis C are the two main causes of HCC [17, 18].

Other emerging causes of chronic liver disease with increasing importance are non-alcoholic fatty liver disease (NAFLD), associated with obesity and type 2 diabetes [19], and liver disease in patients with human immunodeficiency virus (HIV) infection, mainly caused by hepatitis C due to the efficacy of highly active antiretroviral therapy and consequently longer survival of these patients [20, 21].

Spanning a 7-year period (2006–2012) and including fourteen hepatobiliary disease entities, this study was conducted to assess mortality related to liver disease in Portugal compared with mortality from other causes.

Materials and Methods

Mortality data from all main causes of death in Portugal were provided by the National Statistics Institute according to cause (International Classification of Diseases, 10th revision, version 2014), sex, age, and region. The reported causes of death from hepatobiliary disease in Portugal are showed in Table 1.

The National Statistics Institute's statistical confidentiality framework stood as the main limitation of this study. As such, occurrences of less than three deaths were unavailable for study inclusion.

Statistical analysis was conducted using the IBM SPSS® (Version 21) software, and charts and tables were produced using Microsoft Word 2007® and Microsoft Excel 2007®, respectively. To calculate the number of deaths from liver disease in patients with HIV infection, 15% of the total number of deaths from HIV infection were considered to be related to liver disease, as reported in the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study [20].

Results

A total of 18,279 deaths (24.5/100,000) from hepatobiliary disease were reported between 2006 and 2012. The main causes were alcoholic liver disease (ALD) (7.1/100,000), unspecified cirrhosis of liver (UCL) (5.5/

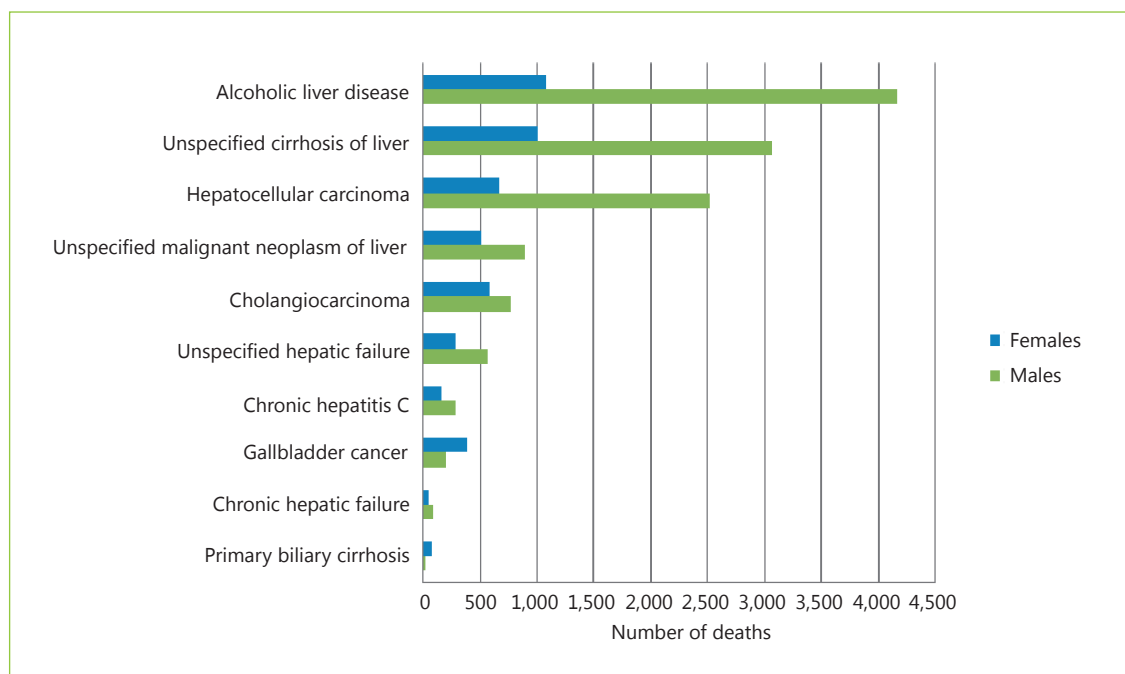


Fig. 2. Number of deaths from hepatobiliary disease by sex in Portugal, 2006–2012.

100,000), and HCC (4.3/100,000) (Fig. 1). When comparing the mortality rates from 2006 to those from 2012, the mortality from ALD and HCC increased by 6 and 66%, respectively, while the mortality from UCL decreased by 26%.

Sex

All-cause hepatobiliary disease mortality was higher in males (72%) compared with females, with a male:female (M:F) ratio of 2.6:1. The three leading causes of death for both sexes were ALD (M: 11.7/100,000; F: 2.8/100,000; M:F ratio: 3.9:1), UCL (M: 8.6/100,000; F: 2.6/100,000; M:F ratio: 3.0:1), and HCC (M: 7.1/100,000; F: 1.8/100,000; M:F ratio: 3.7:1) (Fig. 2).

Age

Considering all causes of hepatobiliary disease included in our study, mortality was highest in males 75–79 years of age (120.1/100,000) and in females ≥85 years of age (44.8/100,000) between 2006 and 2012.

ALD showed greater mortality in the middle-age groups (40–65 years), while mortality from primary neoplasms of the liver and intrahepatic bile ducts occurred predominantly in the elderly (>80 years). Mortality from UCL and HCC occurred predominantly in the 8th and 9th decade of life, respectively (Fig. 3).

Region

Portugal is a country located in Western Europe. The regional distribution of the three main causes of death from hepatobiliary disease in Portugal was as follows:

ALD. Mortality was highest in the archipelago of Madeira (11.3/100,000). In mainland Portugal there was a north-south gradient in mortality rates of 8.4/100,000 and 4.3/100,000, respectively (Fig. 4a).

UCL. Once again, mortality was higher in the archipelago of Madeira (8.8/100,000) compared with mainland Portugal. In mainland Portugal, mortality from UCL was highest in the centre of the country, with a rate of 6.9/100,000, and lowest in the south (4.3/100,000) (Fig. 4b).

HCC. Mortality from HCC was highest in the centre of the country, with rates of around 5.0/100,000, compared to the south with rates of around 3.0/100,000 (Fig. 4c).

Malignant Neoplasm of Liver and Intrahepatic Bile Ducts (C22)

Considering the mortality from the various types of primary neoplasms of the liver and intrahepatic bile ducts, HCC was the most frequent (53.6%), followed by unspecified malignant neoplasm of liver (23.5%) and cholangiocarcinoma (22.7%) (Table 2).

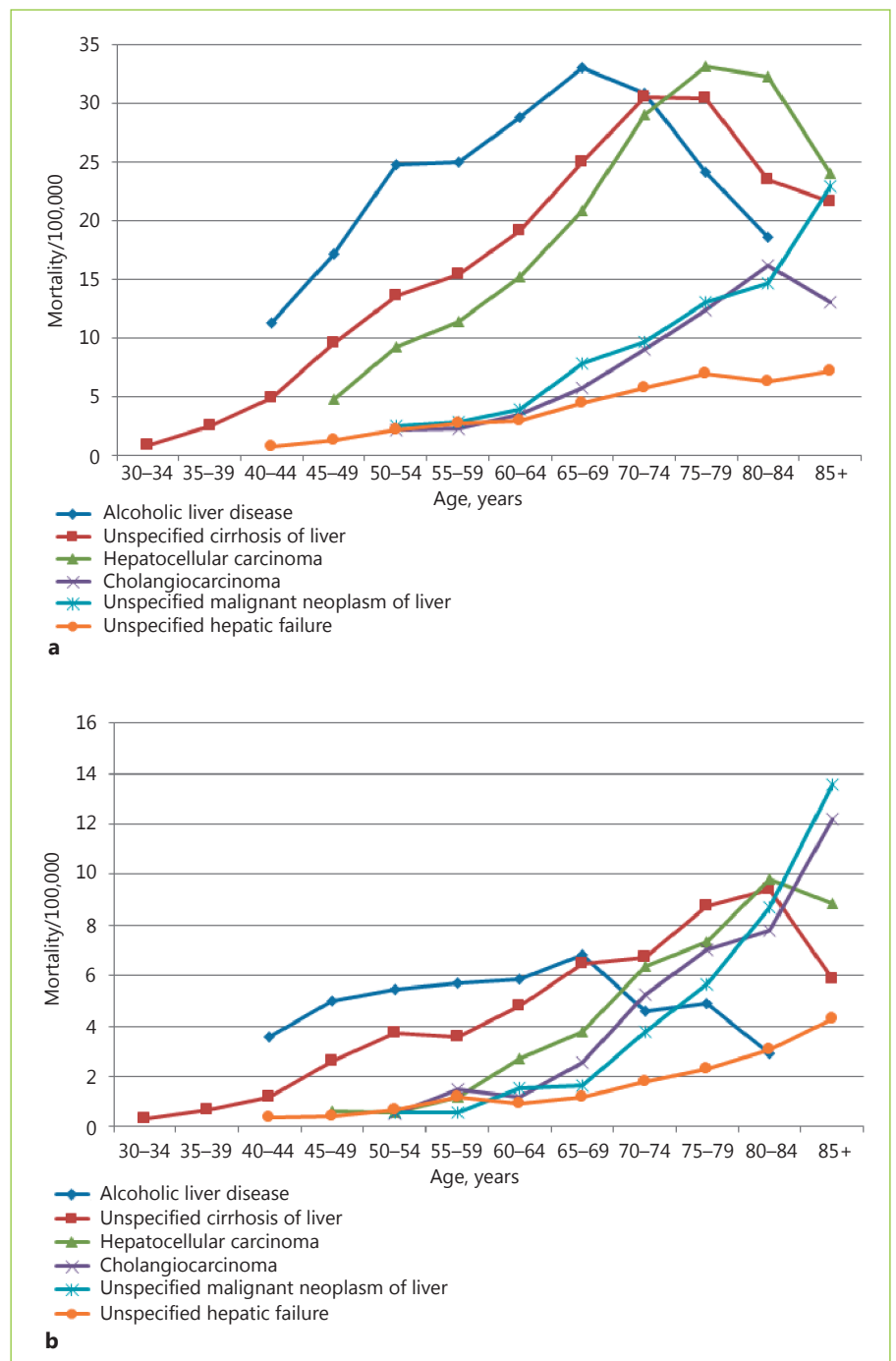


Fig. 3. Mortality/100,000 according to age group in Portugal, 2006–2012 for males (a) and females (b).

Top 10 Causes of Death in Portugal

Hepatobiliary disease was the 8th leading cause of death in Portugal between 2006 and 2012, with a mortality rate of 25.1/100,000, almost equivalent to the 7th leading cause of death, chronic obstructive pulmonary disease (Table 3).

Discussion and Conclusions

Current evidence suggests that the burden of liver-related mortality is increasing [22]. However, there are very few studies that consider mortality from liver disease by aggregating death rates from different causes such as liv-

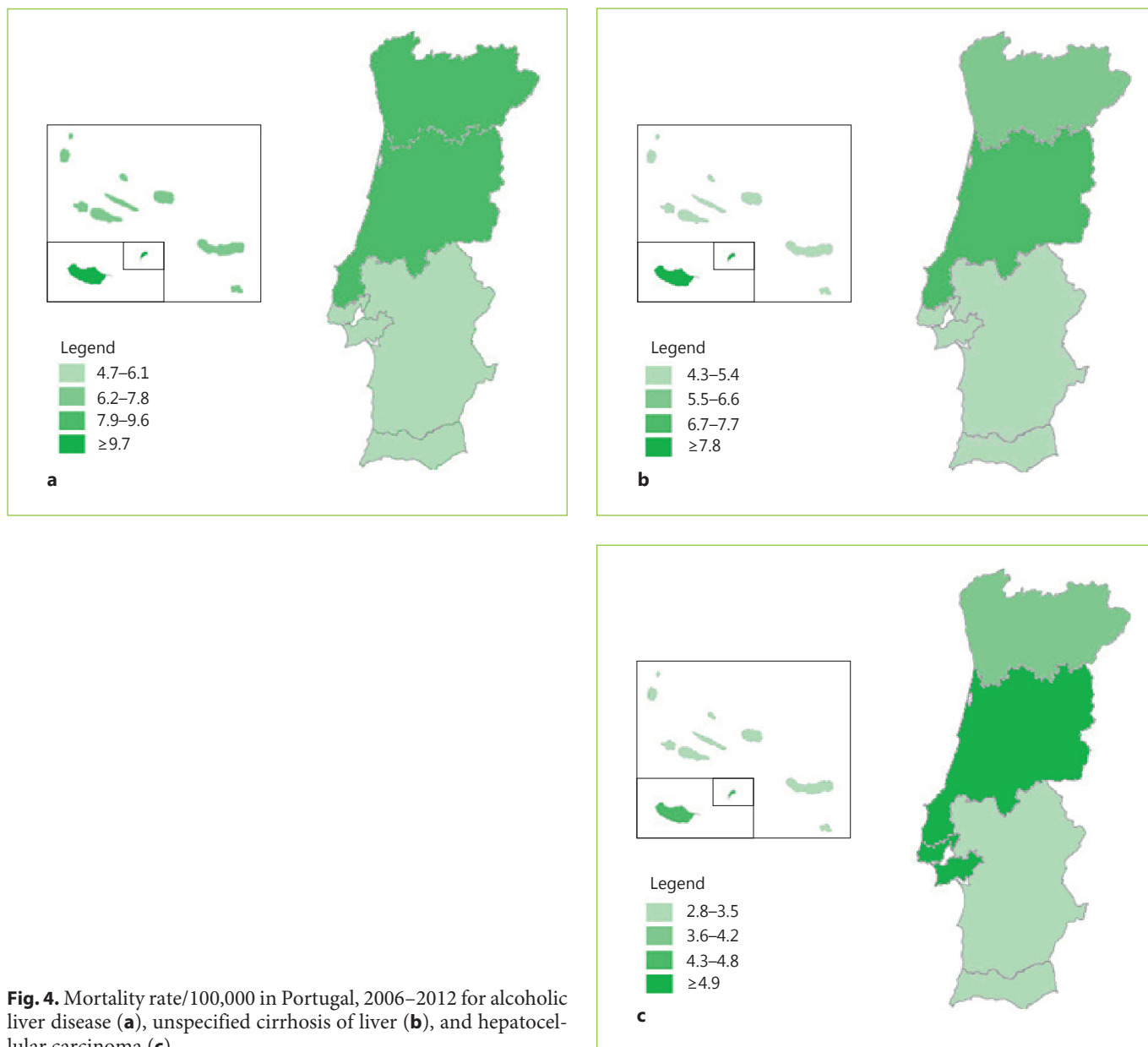


Fig. 4. Mortality rate/100,000 in Portugal, 2006–2012 for alcoholic liver disease (**a**), unspecified cirrhosis of liver (**b**), and hepatocellular carcinoma (**c**).

er cirrhosis, liver cancer, viral hepatitis, and HBV/HCV coinfection with HIV. In this study, in which mortality from fourteen types of hepatobiliary disease was aggregated, the disease was found to be the 8th leading cause of death in Portugal, consistent with results from Europe [6] and Brazil [23].

The main cause of death from hepatobiliary disease in Portugal is ALD (7.1/100,000), which is most predominant in males between 40 and 65 years of age. This was expected, as alcohol consumption in Portugal is higher in males than females [24] and is most common between the

ages of 25 and 54 years (80% of consumers) [25]. It is important to emphasise that ALD in males between 50 and 65 years of age has a mortality rate of 25–30/100,000, and so has the potential of having a severe impact on national productivity and economy [26–28].

The 2nd leading cause of death from liver disease in Portugal is UCL (5.5/100,000), with chronic hepatitis B and C and NAFLD possibly contributing to this category. The mortality from hepatitis B and C is lower than expected when considering the prevalence estimated for the disease in Portugal (1%) [14, 29, 30]. Mortality from

Table 2. Deaths from the different causes of malignant neoplasm of liver and intrahepatic bile ducts in Portugal, 2006–2012

Malignant neoplasm of liver and intrahepatic bile ducts	Number of deaths	%
Hepatocellular carcinoma	3,191	53.6
Unspecified malignant neoplasm of liver	1,400	23.5
Cholangiocarcinoma	1,354	22.7
Other ^a	10	0.2
Total	5,955	100.0

^a Information related to all causes whose mortality values were available.

Table 3. The ten main causes of death (ICD-10 codes) in Portugal, 2006–2012

Causes of death	Number of deaths	Mortality/100,000
1 Cerebrovascular diseases (I60–I69)	99,515	134.8
2 Heart diseases (I20–I25, I30–I33, I39–I52)	95,644	129.6
3 Pneumonia (J12–J18)	37,314	50.6
4 Diabetes mellitus (E10–E14)	31,187	42.2
5 Lung cancer (C32–C34)	26,997	36.6
6 Colorectal cancer (C18–C21)	25,508	34.6
7 Chronic obstructive pulmonary disease (J40–J47)	18,698	25.3
8 Hepatobiliary disease ^a	18,517	25.1
9 Gastric cancer (C16)	16,651	22.6
10 Malignant neoplasms of lymphoid, haematopoietic, and related tissue (C81–C96)	13,541	18.3

ICD-10, International Classification of Diseases, 10th revision. ^a Information related to all causes whose mortality values were available.

NAFLD in Portugal is unknown. However, its burden is probably high due to an increasing prevalence of obesity, which is directly related to the development of NAFLD [31]. The proportion of adults who are overweight or obese in Portugal is known to be rising and has increased from 49.6% in 1995–1998 to 53.6% in 2003–2005 [32].

In Portugal, mortality from HCC increased by 66% between 2006 and 2012. This may be related to the longer survival of patients with liver cirrhosis due to better prevention and treatment, which in turn increases the possibility of developing HCC (by approximately 4% for each additional year of life) [33]. In addition, diagnostic accuracy has improved, mainly due to the widespread use of ultrasonography and determination of α -fetoprotein levels, which has led to better detection of HCC in cirrhotic patients [17].

As expected, HCC is predominant in males due to a higher incidence of liver cirrhosis. Furthermore, there is evidence showing an increased incidence of viral hepatitis in males (M:F ratio: hepatitis B, 1.5:1; hepatitis C, 2:1)

[34] and therefore an increased susceptibility to the development of HCC [35, 36].

In 2007, the countries of the European Union with the highest HCC mortality rates in males were France (6.2/100,000), Spain (4.9/100,000), and Italy (4.0/100,000) [37]. According to this study, the HCC mortality rate in males in 2007 was 5.8/100,000, suggesting that Portugal is among the European countries with the highest mortality from HCC.

With regards to cholangiocarcinoma, the European countries with the highest mortality rates in 2008 included Germany, France, and the United Kingdom (males: 1.2–1.5/100,000; females: 0.8–1.1/100,000) [37]. According to our study, the mortality rate from cholangiocarcinoma in Portugal in the same year was 1.6/100,000 in males and 1.4/100,000 in females. Therefore, Portugal also seems to be one of the European countries with the highest mortality rates from cholangiocarcinoma.

In this study, HCC was the most frequent cause of death from malignant neoplasms of the liver and intrahe-

patic bile ducts (53.6%). Considering that HCC corresponds to 80% of primary tumours of the liver and incidence is almost the same as mortality [38], we expected a higher percentage of deaths from HCC in this group. However, it was observed that 23.5% of all deaths from malignant neoplasms of the liver and intrahepatic bile ducts were coded as unspecified malignant neoplasm of liver, suggesting that HCC is underdiagnosed in Portugal.

Regarding regional distribution, the mortality from liver cirrhosis was highest in the archipelago of Madeira. This is likely to be due to high alcohol consumption and historically high levels of intravenous drug abuse. In mainland Portugal there was a north-south gradient in ALD mortality which is consistent with the pattern of alcohol consumption [25]. The higher mortality rates registered in the north of the country are also related to the location of the reference centres. These centres are located in the north (Porto) and centre (Coimbra and Lisbon) of Portugal and are where many of the patients died.

In conclusion, from 2006 to 2012, hepatobiliary disease was the 8th leading cause of death in Portugal. The main causes were ALD, UCL, and HCC, with the highest predominance in males. In particular, ALD represents an important problem in males between 50 and 65 years old,

with a potential impact on national productivity. Since almost all causes of liver disease are preventable, we believe that this study highlights an urgent unmet need for a strategic policy to prevent liver-related deaths in Portugal.

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Statement of Ethics

This study did not require informed consent nor review/approval by the appropriate ethics committee.

Disclosure Statement

There are no conflicts of interest to declare for this work.

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