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Complications Requiring Hospital Admission and Causes of In-Hospital Death over Time in Alcoholic and Nonalcoholic Cirrhosis Patients

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See editorial on page 8.

Background/Aims: Data on the epidemiology of alcoholic cirrhosis, especially in Asian countries, are limited. We compared the temporal evolution of patterns of alcoholic and nonalcoholic cirrhosis over the last decade. **Methods:** We retrospectively examined the inpatient datasets of five referral centers during 2002 and 2011. The study included patients who were admitted due to specific complications of liver cirrhosis. We compared the causes of hospital admissions and in-hospital deaths between patients with alcoholic and nonalcoholic cirrhosis. **Results:** Among the included 2,799 hospitalizations (2,165 patients), 1,496 (1,143 patients) were from 2002, and 1,303 (1,022 patients) were from 2011. Over time, there was a reduction in the rate of hepatic encephalopathy (HE) as a cause of hospitalization and an increase in the rate of hepatocellular carcinoma. Deaths that were attributable to HE or spontaneous bacterial peritonitis (SBP) significantly decreased, whereas those due to hepatorenal syndrome (HRS) significantly increased over time in patients with alcoholic cirrhosis. However, in patients with nonalcoholic cirrhosis, hepatic failure and HRS remained the principal causes of in-hospital death during both time periods. **Conclusions:** The major causes of in-hospital deaths have evolved from acute cirrhotic complications, including HE or SBP to HRS in alcoholic cirrhosis, whereas those have remained unchanged in nonalcoholic cirrhosis during the last decade. **(Gut Liver 2016;10:95-100)**

Key Words: Cause of death; Complications; Hospitalization; Liver cirrhosis

INTRODUCTION

Liver disease, including cirrhosis, is an important cause of mortality in Korea and worldwide; it was the eighth leading cause of death in 2011 in Korea.[1,2] Liver cirrhosis is the final result of various chronic liver diseases.[3,4] Upon the occurrence of liver decompensation, patients may develop ascites, variceal bleeding, spontaneous bacterial peritonitis (SBP), hepatic encephalopathy (HE), or hepatorenal syndrome (HRS).[5] In Korea, the most common cause of liver cirrhosis is hepatitis B virus (HBV), followed by alcoholism and hepatitis C virus (HCV).[6-8] With the introduction of universal hepatitis B immunization and advancement of antiviral therapies, the prevalence of HBV-associated cirrhosis has declined steadily.[9,10] In contrast, the prevalence of alcoholic cirrhosis is increasing, and has reached 31%.[7,11]

Although the degree of alcoholic liver disease might depend on individual differences in susceptibility to alcohol toxicity, the quantity of alcohol consumed, genetic factors, or associated diseases, continued drinking accelerates the progression of chronic liver injury. Alcohol is the leading cause of liver cirrhosis in the developed world, accounting for 44% of all deaths caused by liver disease in the United States.[12] Despite the growing economic and public health burden of alcoholic cirrhosis,[13] data on the epidemiology of alcoholic cirrhosis are limited in Korea. Moreover, the patterns of cirrhosis complications are expected

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to evolve due to advancement in the management of such complications.

The aim of this epidemiological study was to compare recent trends in the causes of hospital admissions and deaths between patients with alcoholic and nonalcoholic cirrhosis in a Korean cohort of 2,165 patients admitted to the liver services of five referral hospitals.

MATERIALS AND METHODS

1. Patients

A retrospective analysis was conducted using the medical record databases of five referral hospitals in Korea. The International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) was used to identify diagnoses. Patients who had been hospitalized for cirrhosis-related complications including ascites, variceal bleeding, SBP, HE, HRS, or a first diagnosis of hepatocellular carcinoma (HCC) were included. We determined the causes of admission and in-hospital death by reviewing the discharge records. Patients with programmed hospital admissions or a previous history of HCC were excluded. Separate records of patients who were admitted multiple times within the study year were included. Medical records of 2,799 hospital admissions (2,165 patients) were reviewed, with an average of 1.3 hospitalizations per patients. The study population comprised 2,165 patients with decompensated alcoholic or nonalcoholic cirrhosis who had been hospitalized in five referral hospitals in Korea during 2002 or 2011. We defined alcoholic cirrhosis as excessive alcohol consumption of >60 g/day and evidence of liver cirrhosis complications by retrospective chart review. HBV-related liver cirrhosis was recorded on the chart in case of hepatitis B surface antigen had been present. HCV-related liver cirrhosis was documented on the chart in the presence of antibody to HCV and HCV RNA in the serum. Patients with excessive alcohol consumption together with HBV or HCV infection were classified as having liver cirrhosis with a combined cause. This study was approved by the Institutional Ethics Committee of all participating institutions.

2. Statistical analyses

Data are expressed as means±standard deviation for continuous variables or as counts (percentages) for categorical variables. The t-test was used to compare continuous variables, and the chi-square test was used to compare categorical variables. A p-value of <0.05 was considered to indicate statistical significance. SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) was used for the statistical analyses.

RESULTS

1. Baseline characteristics

During 2002, 1,496 hospital admissions were recorded among 1,143 patients (652 with alcoholic cirrhosis and 491 with nonalcoholic cirrhosis). During 2011, 1,303 hospital admissions were recorded among 1,022 patients (571 with alcoholic cirrhosis and 451 with nonalcoholic cirrhosis). Table 1 shows the baseline characteristics of all patients. The mean age of all enrolled patients was higher in 2011 than in 2002 (59.0±11.7

Table 1. Baseline Characteristics of Patients with Alcoholic and Nonalcoholic Cirrhosis during 2002 and 2011

Characteristic	2002				2011			
	Total (n=1,143)	Alcoholic (n=652)	Nonalcoholic (n=491)	p-value	Total (n=1,022)	Alcoholic (n=571)	Nonalcoholic (n=451)	p-value
Age, yr	56.9±12.6	57.3±12.4	56.6±12.8	0.36	59.0±11.7	57.5±10.7	60.9±12.6	<0.0001
Male sex	893 (78.1)	593 (91.0)	300 (61.1)	<0.0001	785 (76.8)	509 (89.1)	276 (61.2)	<0.0001
No. of admissions per patient	1.34±0.79	1.27±0.66	1.45±0.92	<0.0001	1.33±0.81	1.33±0.82	1.33±0.79	0.89

Data are expressed as means±standard deviation for continuous variables or as counts (percentages) for categorical variables.

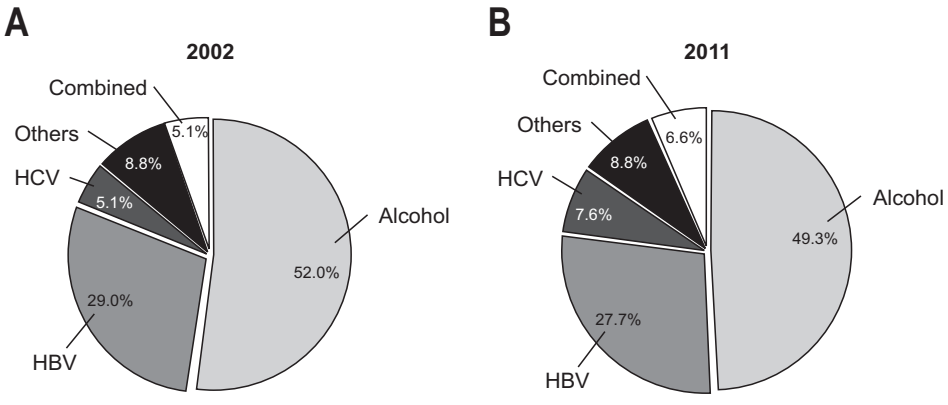

Fig. 1. Comparison of the etiology of liver cirrhosis between (A) 2002 and (B) 2011. In hospitalized patients, alcoholism was the most common cause of liver cirrhosis, followed by hepatitis B infection.
HCV, hepatitis C virus; HBV, hepatitis B virus.

and 56.9±12.6 years, respectively; p<0.0001). The mean age of patients with alcoholic cirrhosis did not change throughout the study decade (57.5±10.7 and 57.3±12.4 years in 2011 and 2002, respectively; p=0.691). However, the mean age of patients with nonalcoholic cirrhosis was 56.6±12.8 years in 2002 and increased to 60.9±12.6 years in 2011 (p<0.0001). A greater number of males than females had alcoholic cirrhosis than nonalcoholic cirrhosis in both 2002 and 2011 (2002: 91.0% vs 61.1%, p<0.0001; 2011: 89.1% vs 61.2%, p<0.0001). Alcoholic cirrhosis was the leading cause of liver cirrhosis (52.0% in 2002, 49.3% in 2011) among patients who had been hospitalized due to cirrhosis complications, followed by HBV-related cirrhosis (29.0% in 2002, 27.7% in 2011) and nonalcoholic, nonviral cirrhosis (8.8% in 2002, 8.8% in 2011) (Fig. 1).

2. Decade-long trends in causes of hospitalization

The most frequent causes of hospital admissions in 2002 were variceal bleeding (31.9%) and HE (21.4%), and those in 2011 were variceal bleeding (35.1%) and ascites (16.6%) (Table 2). The proportions of HE and SBP among the causes of admissions were significantly lower in 2011 than in 2002 (HE: 13.7% vs 21.4%, p<0.0001; SBP: 2.7% vs 5.4%, p<0.0001). On the other hand, the proportions of HCC and HRS among the causes of admissions were significantly higher in 2011 than in 2002 (HCC: 14.0% vs 7.0%, p<0.0001; HRS: 1.9% vs 0.7%, p=0.006). In a separate analysis according to the cause of liver cirrhosis, patients with alcoholic cirrhosis showed a decade-long trend similar to that of patients with nonalcoholic cirrhosis (Table 2, Fig. 2). In the separate analysis according to the study year, variceal bleeding and hepatic failure accounted for more hospitalizations in alcoholic cirrhosis than in nonalcoholic cirrhosis in both 2002 and 2011. Whereas the proportions of HCC and SBP among the causes of admissions were significantly higher in nonalcoholic cirrhosis than in alcoholic cirrhosis at both time periods (Supplementary Table 1).

3. Decade-long trends in causes of in-hospital death

The in-hospital mortality rate was 8.6% in 2002 and 9.1%

Table 2. Decade-Long Trends in the Causes of Hospital Admissions

Causes of hospital admissions	Total			Alcoholic			Nonalcoholic		
	2002 (n=1,496)	2011 (n=1,303)	p-value	2002 (n=806)	2011 (n=725)	p-value	2002 (n=690)	2011 (n=578)	p-value
Variceal bleeding	477 (31.9)	458 (35.1)	0.07	285 (35.4)	268 (37.0)	0.51	192 (27.8)	190 (32.9)	0.05
Hepatic encephalopathy	320 (21.4)	178 (13.7)	<0.0001	180 (22.3)	113 (15.6)	<0.0001	140 (20.3)	65 (11.2)	<0.0001
Ascites	267 (17.8)	216 (16.6)	0.38	121 (15.0)	119 (16.4)	0.45	146 (21.1)	97 (16.8)	0.05
Hepatic failure	236 (15.8)	208 (16.0)	0.89	159 (19.7)	135 (18.6)	0.58	77 (11.2)	73 (12.6)	0.42
Hepatocellular carcinoma	104 (7.0)	183 (14.0)	<0.0001	38 (4.7)	62 (8.6)	0.002	66 (9.6)	121 (20.9)	<0.0001
Spontaneous bacterial peritonitis	81 (5.4)	35 (2.7)	<0.0001	17 (2.1)	11 (1.5)	0.39	64 (9.3)	24 (4.2)	<0.0001
Hepatorenal syndrome	11 (0.7)	25 (1.9)	0.01	6 (0.8)	17 (2.3)	0.01	5 (0.7)	8 (1.4)	0.25

Data are presented as the number of hospitalizations (%).

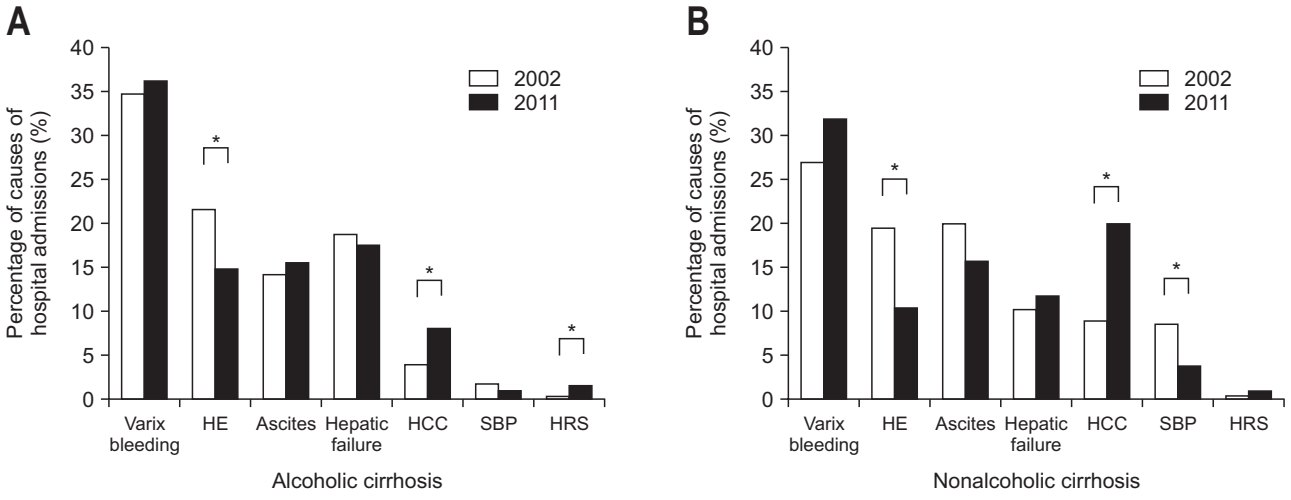

Fig. 2. Decade-long trends in the causes of hospital admissions among patients with (A) alcoholic cirrhosis versus (B) nonalcoholic cirrhosis. HE, hepatic encephalopathy; HCC, hepatocellular carcinoma; SBP, spontaneous bacterial peritonitis; HRS, hepatorenal syndrome. *p<0.05.

in 2011. Hepatic failure (25.4%) and variceal bleeding (22.3%) accounted for the majority of in-hospital deaths in 2002, while HRS (34.7%) and hepatic failure (30.5%) were the most frequent causes of in-hospital deaths in 2011. Among the causes of in-hospital death, HE (9.3% vs 22.3%) and SBP (5.1% vs 13.1%) were significantly less frequent in 2011 than in 2002. On the contrary, the proportion of HRS (34.7% vs 16.9%) among all causes of death increased over the study decade (Table 3). In a separate analysis according to the cause of liver cirrhosis, this trend was not noted in patients with nonalcoholic cirrhosis, but was present in patients with alcoholic cirrhosis. Hospitalized patients with alcoholic cirrhosis died of acute cirrhotic complications such as variceal bleeding, HE, or SBP in 2002; however, hepatic failure or HRS were major causes of in-hospital death in 2011 (Table 3, Fig. 3A). Among patients with nonalcoholic cirrhosis, hepatic failure and HRS remained the principal causes of in-hospital death from 2002 through 2011 (Table 3, Fig. 3B). In the separate analysis according to the study year, the proportion of HE among causes of in-hospital death was higher in alcoholic cirrhosis in 2002, whereas that was lower in alcoholic cirrhosis than in nonalcoholic cirrhosis in 2011 (Supplementary Table 2).

DISCUSSION

Despite the substantial burden of alcoholic liver cirrhosis on public health and the economy, few studies have investigated the change in the epidemiology of alcoholic liver cirrhosis over time in Korea. In this study, we found that the proportion of HE and SBP accounting for hospitalization decreased over time and that variceal bleeding and hepatic failure accounted for more hospitalizations in alcoholic cirrhosis whereas the proportions of HCC and SBP accounting for hospitalization were higher in nonalcoholic cirrhosis in both 2002 and 2011. We also found that the major causes of in-hospital death among patients with alcoholic cirrhosis evolved from acute cirrhotic complications, including HE or SBP, in 2002 to hepatic failure or HRS in 2011.

In Korea, the most common cause of liver cirrhosis is reportedly HBV, followed by alcoholism and HCV.[6-8] Alcoholism was the predominant cause among inpatients with liver cirrhosis who had been hospitalized due to complications of cirrhosis in the present study. Possible explanations for this discrepancy

Table 3. Decade-Long Trends in the Causes of In-Hospital Death

Causes of in-hospital death	Total			Alcoholic			Nonalcoholic		
	2002 (n=130)	2011 (n=118)	p-value	2002 (n=62)	2011 (n=63)	p-value	2002 (n=68)	2011 (n=55)	p-value
Variceal bleeding	29 (22.3)	24 (20.3)	0.93	16 (25.8)	14 (22.2)	0.64	13 (19.1)	10 (19.2)	0.90
Hepatic encephalopathy	29 (22.3)	11 (9.3)	0.01	19 (30.6)	2 (3.2)	<0.0001	10 (14.7)	9 (16.4)	0.80
Spontaneous bacterial peritonitis	17 (13.1)	6 (5.1)	0.03	7 (11.3)	1 (1.6)	0.03	10 (14.7)	5 (9.1)	0.34
Hepatic failure	33 (25.4)	36 (30.5)	0.37	12 (19.4)	21 (33.3)	0.08	21 (30.9)	15 (27.3)	0.66
Hepatorenal syndrome	22 (16.9)	41 (34.7)	0.001	8 (12.9)	25 (39.7)	0.001	14 (20.6)	16 (29.1)	0.28

Data are presented as the number of deaths (%).

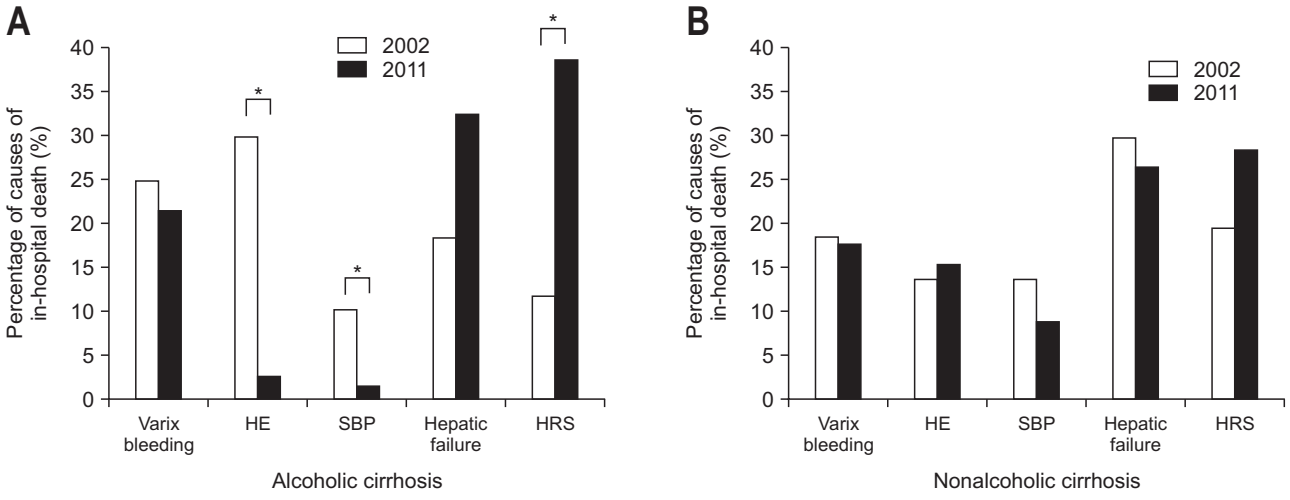

Fig. 3. Decade-long trends in the causes of in-hospital death. (A) Alcoholic cirrhosis and (B) nonalcoholic cirrhosis.
HE, hepatic encephalopathy; SBP, spontaneous bacterial peritonitis; HRS, hepatorenal syndrome. *p<0.05.

may reside in differences in the hospitalization setting and geographical region. Moreover, the increase in the prevalence of alcoholic cirrhosis with a steady decrease in the prevalence of HBV-associated cirrhosis[7,11] might contribute to this finding. With regard to the epidemiology of cirrhosis in Korea, the prevalence of HBV-related liver cirrhosis is expected to decrease with the introduction of vaccination and potent antiviral agents. Despite the lack of nationwide data on the epidemiology of alcoholic liver cirrhosis, it is speculated that the proportion of patients with alcoholic cirrhosis will increase considering the increase in the quantity of per capita alcohol consumption from 5.02 kg in 2001 to 5.64 kg in 2004.[14]

Among the causes of hospitalization, variceal bleeding, HE, and ascites comprised a large proportion of hospital admissions in 2002. Although these complications remain major causes of hospital admissions, the proportion of HE decreased in 2011. Increasing knowledge of the pathophysiology of liver cirrhosis and improvement in the prevention of cirrhosis complications might contribute to a reduction in the proportion of HE among hospitalized patients. On the other hand, HCC has become a common cause of admission in cirrhotic patients. Early detection by virtue of increased HCC surveillance[15,16] or an aging cohort of patients with HBV or HCV[15,17] could partly explain this finding.

Our report demonstrated a significant downward trend of deaths attributable to HE or SBP. The recent reduction in mortality from HE or SBP is associated with the introduction of rifaximin[18] or albumin and cephalosporin.[19,20] According to the results of the stratified analysis of alcoholic versus nonalcoholic cirrhosis, this overall trend was more prominent in patients with alcoholic cirrhosis. The acute insult is often superimposed on the chronic decompensation in patients with alcoholic liver cirrhosis because of continued alcohol drinking. Therefore, acute complications such as variceal bleeding, HE, or SBP were major causes of death in patients with alcoholic cirrhosis 10 years ago. With recent advances in the management of cirrhosis complications, these acute complications have been well controlled. Still, complications such as HRS or hepatic failure are associated with high mortality, and liver transplantation is the only curative treatment in such cases.[21] The in-hospital mortality rate did not show a statistically significant decreasing trend despite the improvement in hospital care. It seems that the causes of in-hospital death changed from acute to terminal complications, which cannot be treated by methods other than liver transplantation, over the last decade.

This study has some limitations. First, it was difficult to identify the underlying complications that lead to death because of the overlapping complications of cirrhosis. Second, selection bias might have been present because of the retrospective design using codified electronic medical records. Third, we did not consider the degree of liver dysfunction, including the Child-Pugh classification or the Model of End-stage Liver Disease, other than cirrhosis complications. Fourth, this retrospective study had collected data on the event of death during hospital admission. Therefore, we were unable to compare the survival curve between alcoholic cirrhosis and nonalcoholic cirrhosis. Fifth, we did not perform a liver biopsy to confirm the alcoholic cirrhosis. Given the absence of definitive diagnostic criteria for the pathologic diagnosis of alcoholic cirrhosis, the issues regarding the representativity of liver biopsy and the invasiveness, we used clinical diagnosis of alcoholic cirrhosis. Finally, the enrolled patients did not represent the entire population of hospitalized patients with cirrhosis in Korea.

Nevertheless, this study has some strengths. A relatively large number of patients were enrolled in the analysis. We also investigated the trend of complications and in-hospital deaths among cirrhotic patients who were hospitalized in five referral centers, stratified according to alcoholic and nonalcoholic cirrhosis. Several single-center retrospective studies have reported the epidemiology of alcoholic liver cirrhosis, but the results could not be directly compared. Moreover, few studies have compared the epidemiology of alcoholic and nonalcoholic cirrhosis.

In conclusion, HE and SBP accounted for less hospitalization while the proportions of HCC and HRS increased over time in alcoholic and nonalcoholic cirrhosis patients. There was a decrease in the proportion of death attributable to acute cirrhotic complications, including HE or SBP, with the simultaneous increase in the proportion of HRS or hepatic failure among causes of in-hospital deaths in alcoholic cirrhosis. Whereas HRS or hepatic failure remained leading causes of in-hospital deaths in nonalcoholic cirrhosis during the last decade.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Supplementary Table 1. Causes of Hospital Admissions according to the Study Year

Causes of hospital admissions	2002 (n=1,496)			2011 (n=1,303)		
	Alcoholic (n=806)	Nonalcoholic (n=690)	p-value	Alcoholic (n=725)	Nonalcoholic (n=578)	p-value
Variceal bleeding	285 (35.4)	192 (27.8)	0.001	268 (37.0)	190 (32.9)	0.069
Hepatic encephalopathy	180 (22.3)	140 (20.3)	0.185	113 (15.6)	65 (11.2)	0.014
Ascites	121 (15.0)	146 (21.2)	0.001	119 (16.4)	97 (16.8)	0.458
Hepatic failure	159 (19.7)	77 (11.1)	<0.0001	135 (18.6)	73 (12.6)	0.002
Hepatocellular carcinoma	38 (4.7)	66 (9.6)	<0.0001	62 (8.6)	121 (20.9)	<0.0001
Spontaneous bacterial peritonitis	17 (2.1)	64 (9.3)	<0.0001	11 (1.5)	24 (4.2)	0.003
Hepatorenal syndrome	6 (0.8)	5 (0.7)	0.604	17 (2.3)	8 (1.4)	0.146

Data are presented as the number of hospitalizations (%).

Supplementary Table 2. Causes of In-Hospital Deaths according to the Study Year

Causes of in-hospital deaths	2002 (n=130)			2011 (n=118)		
	Alcoholic (n=62)	Nonalcoholic (n=68)	p-value	Alcoholic (n=63)	Nonalcoholic (n=55)	p-value
Variceal bleeding	16 (25.8)	13 (19.1)	0.403	14 (22.2)	10 (18.2)	0.651
Hepatic encephalopathy	19 (30.6)	10 (14.7)	0.036	2 (3.2)	9 (16.3)	0.023
Spontaneous bacterial peritonitis	7 (11.3)	10 (14.7)	0.611	1 (1.6)	5 (9.1)	0.096
Hepatic failure	12 (19.4)	21 (30.9)	0.160	21 (33.3)	15 (27.3)	0.550
Hepatorenal syndrome	8 (12.9)	14 (20.6)	0.349	25 (39.7)	16 (29.1)	0.250

Data are presented as the number of deaths (%).