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ECONOMIC BURDEN OF CIRRHOSIS IN CATALONIA:A POPULATION-BASED ANALYSIS

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List of Abbreviations:

ICD-9CM: Clinical Modification of the International Classification of Diseases, 9th Revision codes

DRG: Diagnosis-related group

AMG: Adjusted morbidity Groups

ANOVA: Analysis of variance

CI: confidence interval

ABSTRACT

Backgrounds: Cirrhosis is a chronic disease with high morbidity and mortality. Few studies have evaluated healthcare resource use in patients with cirrhosis.

Objective: We aimed to describe the population-level distribution of healthcare resource use and expenditures in a non-selected population of cirrhotic patients stratified in function of whether their disease was compensated or decompensated and in function of comorbidity burden.

Methods: This is a population study included all known patients with cirrhosis in Catalonia, Spain, on December 31, 2012. The inclusion criteria were all cirrhotic patients according to ICD-9 over 18 years old. We evaluated healthcare resource use and expenditure during 2013, taking into account the presence of decompensation before or during 2012.

Results: We documented 34,740 patients diagnosed with cirrhosis (58.7% men; mean age 61.8±14 years), yielding a prevalence of 460 per 100,000 inhabitants. Annual mortality was 9.1%. During 2013, healthcare expenditures on cirrhotic patients totaled €142.1 million (€4,234 per patient), representing 1.8% of the total 2013 healthcare budget of Catalonia. Hospitalization costs accounted for 35.1% of the total expenditure, and outpatient care accounted for 22.4%. Multivariable logistic regression identified morbidity burden, HIV+, hospitalization, and emergency room visits during 2012 as independent predictors of expenditure > 85th percentile (area under the receiver operating curve, 0.88 (95%CI:0.883–0.893) P<0.001).

Conclusions: Cirrhosis accounts for a high proportion of healthcare resource usage and expenditures; hospitalization accounted for the greatest expenditures.

electronic count: 228

Strengths and limitations of this study:

- We analyzed the use of medical resources and healthcare expenditures in cirrhotic patients in function of whether their disease was compensated or decompensated.
- We used a population-based health risk assessment tool to calculate individuals' level morbidity burden and analyzed the impact of multimorbidity on resource use and costs.
- Our results can help in planning resource allocation and implementing preventive policies, especially in public health systems.
- The use of a general population database minimized selection bias and allowed us to analyze real world population. However, using administrative data to identify cirrhotic patients can lead to misdiagnosis

INTRODUCTION:

Cirrhosis is a late stage in progressive liver disease of varying etiologies. The prevalence of cirrhosis among older adults is not well known, but is expected to increase, in part due to the rising incidence of nonalcoholic fatty liver disease and the aging of the hepatitis C population[1–3]. In fact, there is an increasing trend in the diagnosis of chronic liver disease and its decompensations and complications (including hepatocellular carcinoma)[4]

The interval between the compensated phase of cirrhosis and the development of complications (decompensated cirrhosis) is often long, with a reported median survival of 12 years[5,6]. Compared to an age-matched patients without cirrhosis, patients with cirrhosis have worse health and more comorbid conditions resulting in greater use of healthcare services, including more hospital visits, nursing home stays, and physician visits [2].

Chronic hepatitis C virus infection is one of the main causes of cirrhosis, and it is the most common indication for liver transplantation in Spain and worldwide[7,8]. Hepatitis C infection not only affects the liver, but is also related with hypertension and other cardiovascular diseases, chronic renal impairment, and diabetes mellitus. Some studies have estimated the costs of hepatitis C infection without, however, analyzing the impact of complications of advanced liver disease [4].

Knowing the impact of decompensated disease on outcomes and on the cost of treating advanced liver disease is important for planning resource allocation and preventive strategies, especially in a public health system[8]. Because of its

importance in public health, a growing number of publications address chronic liver disease [2,8–11].

This study aimed to describe global healthcare resource use and expenditures in a non-selected population of cirrhotic patients stratified into compensated vs. decompensated disease.

MATERIALS AND METHODS

Data Source and Study Design

We analyzed healthcare resource use and expenditures in 2013 by patients with cirrhosis residing in Catalonia, an autonomous region in Northeast Spain with 7,553,650 inhabitants (density, 232.8 inhabitants/km^2). The regional health department, named CatSalut, provides universal healthcare coverage to all residents and collects detailed information on healthcare usage, including information from the minimum basic dataset registered by healthcare units (e.g., hospitals, primary care centers, nursing facilities, and mental health centers). CatSalut also collects information on drug prescription and billing for services (e.g., outpatient visits to specialists, emergency department visits, non-urgent medical transportation, outpatient rehabilitation, home oxygen therapy, and dialysis). This Catalan Health Surveillance System (CHSS) contains 529 million diagnoses, 440 million contacts with the various public health services, and 519 million prescriptions dispensed by pharmacies. Its automated data validation system checks the consistency of the data and identifies potential errors. Moreover, as this information is used for healthcare provider payment purposes,

periodic external audits are carried out to ensure the quality and reliability of the data.

Information from private health centers was not available for analysis. Nevertheless, private centers accounted for only 205,385 (21%) of 978,024 hospitalizations for all causes in Catalonia in 2013. Moreover, private centers rarely hospitalize cirrhotic patients: in 2013, of 2,878 unplanned hospitalizations of cirrhotic patients, 2,727(94.8%) took place in public hospitals and only 151 (5.2%) in private hospitals.

Selection of Patients

This retrospective cohort study included all residents of Catalonia aged 18 years or older diagnosed with cirrhosis on or before 31 December 2012. The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9CM) codes were used to identify cases with cirrhosis (Codes: 571.2 and 571.5) (see Suppinfo.Appendix1) as well as complications of cirrhosis.

We defined hepatic decompensation as an unscheduled hospital admission in which the reason of income is due to hepatic encephalopathy, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, or hepatic complications such as hepatocellular carcinoma, esophageal varices, or portal hypertension. We divided patients into three groups:

- Compensated group: cirrhotic patients who had not had any episodes of hepatic decompensation before 2013,
- Previous decompensation group: patients who had had at least one episode of hepatic decompensation before 2012 but none during 2012,

- Recent decompensation group: patients who had at least one episode of hepatic decompensation during 2012.

Calculation of Expenditure

The primary outcome variable of the study was expenditures related to healthcare resource use in 2013. In Catalonia, expenditures for healthcare and pharmacy services are normally directly attributed to each patient through their personal health identification number. Expenditures for primary care are calculated indirectly from a standard price per visit weighted by attending professional (physician or nurse) and site of assistance. Expenditures for hospital care are weighted by diagnosis-related groups (DRG). Expenditures for in-patient care at hospitals, skilled nursing facilities, and mental health centers are calculated according to length of stay (suppinfo: Table 1S shows the average price by activity in Catalonia). The cost are attribute to each person through the personal identification code that is assigned in the public sanitary system.

The prices used in the calculations are the rates that CatSalut pays healthcare providers, which are published annually in the Official Gazette of the Government of Catalonia.

CatSalut's budget for 2013 was 8,085 million Euros, of which €7,885 million (97.5%) was devoted to healthcare services. Emergency medical transport and screening for breast and colon cancer accounted for the largest proportion of expenditures that were not individually allocated. The healthcare services in CatSalut's morbidity database accounted for €7,502 million (€ 968 per capita), which represents 95.1% of CatSalut's expenditure on health services.

In this population-based study, the methods used allowed us to analyze the expenditures on patients with cirrhosis, but not the costs attributable only to the disease itself. Thus, we calculated the total healthcare expenditure per person per year (in euros) for patients with cirrhosis (including cirrhosis-related care and care related to co-morbidities), rather than the expenditure specifically associated with cirrhosis care. This approach enabled a comprehensive analysis of healthcare expenditures in this group of complex patients. To account for shorter follow-up periods due to deaths, time at risk was calculated in days from 31 December 2012 to the date of death (or 365 days otherwise) and transformed to years. Thus, the unit of analysis is not the patient but rather the patient/year.

Assessment of predictors of increased expenditure

We also sought to identify independent predictors associated with yearly expenditures greater than or equal to the 85th percentile of the distribution in the study population. This analysis included only patients who survived the whole study period (n=32,214). Predictors assessed were age, sex, co-morbidities included in the Charlson Index[12,13], previous healthcare utilization, and a novel population-based health risk assessment tool deployed in Catalonia, the Adjusted Morbidity Grouper (GMA), which is used to calculate an individual's morbidity burden [14]. The GMA categorizes each patient in a risk stratification pyramid with five strata:

- Basal risk stratum: comprising individuals with minimum morbidity burden; 50% of individuals in the overall population of Catalonia (but 0% of cirrhotic patients) fall into this stratum.

- Low risk stratum: comprising individuals with low level complexity; 30% of individuals in the overall population of Catalonia (but 22.2% of cirrhotic patients) fall into this stratum.
- Moderate risk stratum: comprising individuals with higher complexity than the previous risk stratum; 15% of individuals in the overall population of Catalonia (but 35.6% of cirrhotic patients) fall into this stratum.
- High risk stratum: comprising individuals with a greater morbidity burden than the previous stratum; 4% of individuals in the overall population of Catalonia (but 30.6% of cirrhotic patients) fall into this stratum.
- Very high-risk stratum: comprising individuals with the highest morbidity burden; 1% of individuals in the overall population of Catalonia (but 11.6% of cirrhotic patients) fall into this stratum.

Statistical analysis

Quantitative variables are reported as means±standard deviations. For the univariate analysis, we used chi-square tests to compare qualitative variables and analysis of variance (ANOVA) to compare quantitative variables. To identify independent predictors of increased healthcare expenditure, we used multivariable logistic regression. Variables were entered in the model one by one and retained when their significance was <0.10. To evaluate the discriminatory ability of the resulting predictive model for identifying cirrhotic patients with healthcare expenditures ≥85th percentile, we calculated the area under the receiver operating characteristic (ROC) curve[15]. Statistical analyses were performed using SPSS software, version 18.0. All statistical tests and

confidence intervals (CI) were constructed with a type I error level of 5%, and P-values <0.05 were considered significant.

Ethics

Informed consent and ethics committee approval were not required because the study used retrospective data from administrative databases and patients were anonymous to the researchers.

RESULTS

Demographics of included patients

We documented 34,740 patients in Catalonia with cirrhosis on December 31, 2012 (460 per 100,000 inhabitants); of these 25,299 (72.8%) had never had any episodes of hepatic decompensation (Compensated group), 5,393 (15.5%) had had at least one episode of decompensation of their liver disease before 2012 (Previous decompensation group), and 4,048 (11.7%) had presented at least one hepatic decompensation during 2012 (Recent decompensation group). In the entire group, mean age was 61.2±14 years and 41.8% were women; however, the proportion of women decreased with worsening disease (44.8% in the Compensated group, 33.8% in the Previous decompensation group, and 33.4% in the Recent decompensation group).

Patients with advanced liver disease had more comorbidities, and their comorbidities were more severe than those with less advanced disease. There were no significant differences in dementia or depression between groups. (Table 1; see also Table 2S)

Alcohol abuse, hepatitis C infection and drugs (including not only cocaine, cannabis, opioids, psychostimulants, amphetamines or other hallucinogenic susbtances (sniffing glue,absinthe ...) if not also sedatives, anxiolytics and hypnotics..) were more common in patients who had liver decompensation.

Compared to the Compensated group, mortality during 2013 was two times higher in the Previous decompensation group and more than four times higher in the Recent decompensation group.

Use of Health Resources

The overall rate of hospitalizations was 44.4 per 100 pacients; the rate increased with severity (29.2 in the Compensated group, 60.8 in the Previous decompensation group, and 117.9 in the Recent decompensation group; p<0.0001) (Table 2). Likewise, the mean length of hospitalization increased from 1.8 days in compensated patients to 4.5 days in previously decompensated patients to 9.6 days in recently decompensated patients.

The rate of hospital admissions from the emergency room in the entire group was 27 per 100 pacients, being16.5 in the Compensated group, 37.8 in the Previous decompensation group, and 78.3 in the Recent decompensation group (p< 0.0001) Whereas 33.8%of the patients in the Compensated group presented at the emergency department at least once and 15.7% more than once, 45.5% of those in the Previous decompensation group presented at least once and 25.7%more than once, and 61.4% of those in the Recent

decompensation group presented at least once and 38.8% more than once (Table 2).

Similarly, the number of gastroenterology outpatient visits significantly increased with hepatic decompensation. The number of outpatient visits to other departments also increased, but the difference did not reach statistical significance.

All patients had frequent contact with primary care physicians and/or nurses; the number of primary care visits increased with decompensation (11.8 in the Compensated group, 13.4 in the Previous decompensation group, and 16.5 in the Recent decompensation group; $p<0.0001$). The rate of outpatient visits to mental health centers and the rate of psychiatric hospitalization did not differ among groups. Moreover, the sicker patients were, the more they required social services from convalescence centers, intermediate- or long-stay centers, and palliative care centers

Assessment of healthcare expenditure

During 2013, a total of €142.1 million was spent in the care of cirrhotic patients in Catalonia (1.8% of the total 2013 healthcare budget), representing an average expenditure of €4,234 per patient/year.

Figure 1 displays the distribution of healthcare-related expenditures in cirrhotic patients and in the general population of Catalonia. In cirrhotic patients, the main source of expenditure was hospitalization (for all causes), which accounted for 35.1% of the total; pharmacy costs accounted for 30%, primary care for 11.8% and hospital outpatient care for 10.6%. In contrast, in the

general population the main source of expenses were hospitalization (27.3%), pharmacy (26.1%), primary care (23.2%) and hospital outpatient care (10.7%).

Figure 2 shows the distribution of healthcare-related expenditures in cirrhotic patients, stratified by age group. Despite some differences in resource use and expenditure among the different age groups, hospitalization accounted for the greatest expenditure in all groups.

Total medical expenditure was significantly higher for patients in the Recent decompensation group than for those in the Previous decompensation and compensated group. In the Recent decompensation group, hospitalization was the main expenditure, accounting for more than half of all costs (Figure 3). By contrast, the total expenditure in the Compensated group was divided nearly equally among, pharmacy, hospitalization and outpatient care (hospital and primary care). The distribution of expenditures in the Previous decompensation group lay between those of the other two groups. Figure 3 also shows the distribution of expenditures in 2013 in patients in the Recent decompensation group according to the type of hepatic decompensation occurring in 2012; hepatorenal syndrome, followed by spontaneous bacterial peritonitis and hepatic encephalopathy, generated much higher expenditures than other complications, mainly due to hospitalization.

In cirrhotic patients, the average healthcare expenditure increased with the number of chronic comorbidities, from €773/year in patients with one comorbidity to €14,853/year in those with >9 comorbidities. The GMA stratum

was higher in patients with more comorbidities, and expenditures increased exponentially with increasing GMA strata, from less than €900 for patients in the low risk stratum to more than €15,000 for those in the very high risk stratum (Figure 4).

In patients with lower healthcare resource use (those with expenditures lower than the 85th percentile), expenditures were nearly equally distributed among primary care, pharmacy, and hospitalization. In patients with the highest healthcare resource use, hospitalization accounted for nearly half all expenditures; total healthcare expenditure in this group was ten times higher (€17,822 vs€1,806 patient/year) than in patients with lower resource use.

Table 3 reports the multivariable logistic regression analysis to identify predictors of high expenditure. Morbidity burden (GMA stratum), HIV+, hospitalization, and emergency room visits during 2012 were associated with expenditures greater than or equal to the 85th percentile (i.e., > €7,275 per patient). The area under the ROC curve for identifying patients with expenditures greater than or equal to 85th percentile was 0.888 (95% CI: 0.883–0.893), P <0.001.

DISCUSSION

In our study, liver cirrhosis had an important impact on healthcare expenditures, and expenditures on hospitalization and pharmacy accounted for the largest proportion of costs associated with treating cirrhotic patients. To our knowledge, this is the first poblational study to quantify the total economic impact of

cirrhosis in relation to the hepatic decompensation and to determine the distribution of costs (including all primary care attention and nursing skills, mental health, physical therapy,...) in treating patients with this condition.

This population-based study conducted in Catalonia included around 7,500,000 million people, which could be comparable to some European countries which have similar number of inhabitants.

In recent years, many studies have estimated the economic burden of hepatitis and cirrhosis[16] because these conditions are associated with high morbidity, mortality, and economic costs. One of them[17] analyze the cost over the last year of life in patients with an end stage liver disease but it's not a poblational study like ours. Another study [10] described the direct costs related to hospital admissions in these disease. In our study, we included all the expenses of the illness (during hospital admission and afterwards).

There's one study which analyzed direct and indirect cost [18] of chronic liver disease which includes all the patients and not only cirrhotic ones.

Liver cirrhosis leads to 800,000 deaths every year, representing 1.3 % of all deaths worldwide. According to the World Health Organization, cirrhosis is one of the eighteen causes of death[11]. Five-year survival is 36% in alcoholic cirrhosis and 14% in nonalcoholic cirrhosis [11]. We found that mortality increased significantly in patients who had a recent hepatic decompensation, and the risk of mortality increased nearly 20% in patients with a decompensation in the previous 12 months.

The total cost of treating cirrhotic patients in Catalonia in 2013 was almost €150 million (€4,234 per patient). Hospitalization remains the main source of healthcare-related expenditure, followed by medication, although hospital mortality has decreased in recent years[16]. Patients with more advanced liver disease required more healthcare (more days hospitalized, emergency visits, and primary care visits - which include prescriptions-) and more medication, generating greater expenditures. In patients with cirrhosis, the probability of dying within a year of a hepatic decompensation is 34%[17]. In our study, mortality was nearly 2.3 times higher in patients with a recent decompensation than inpatients who had gone at least a year since a prior decompensation and 4.5 times higher than those who had never had a decompensation.

This large database allowed us to calculate the morbidity burden using the GMA[18]and to stratify the risk of morbimortality. In our population, morbidities were common, and greater severity of liver disease was associated with higher morbidity burden (>75% of all patients were in moderate or higher risk strata: 72.2% in the Compensated group, 90.3% in the Previous decompensation group, and 95.5% in the Recent decompensation group). Moreover, expenditures increased with increasing GMA strata, so controlling comorbidities is one way to reduce costs.

Another way to reduce costs is to modify the natural history of the liver disease. Studies that have analyzed the direct and indirect costs of treating hepatitis C infection point out that costs rise with the natural history of the disease [17,19,20]. New antiviral agents against hepatitis C have modified the natural history of the disease, but the impact of these agents on the overall cost of

treating patients with hepatitis C infection will not become clear until a few years have passed [21].Nevertheless, our results suggest that this impact is likely to be significant because expenditures in patients with recent hepatic decompensation totaled more than twice those in patients who had not had a decompensation for at least one year and more than 3 times those in patients with a compensated cirrhosis.

Although some studies have analyzed the costs caring for other diseases such as diabetes mellitus [22]or heart failure [18], to our knowledge, this is the first population-based study to analyze morbidity and costs in patients with liver disease in function of hepatic decompensation. Although several studies have evaluated some aspects involved in caring for cirrhotic patients (hospitalization, care giving hours [2], our study analyzed overall costs, including expenditures on skilled nursing facility, primary care, and mental health.

Limitations: The use of a general population database minimized selection bias and allowed us to analyze real world population. However, using administrative data to identify cirrhotic patients can lead to misdiagnosis. Moreover, this administrative database did not include important information such as the etiology of cirrhosis (although alcohol consumption and/or hepatitis C infection are recorded in the database) and other important clinical data for characterizing and understanding the study population and the evolution of the disease. Due to this, we can't calculate classical scores such as MELD, Child-Pugh or ACLF.

Patients' need for social services increase when liver disease becomes decompensated; however, the costs associated with this increase are difficult to quantify and vary widely among health systems, so caution is warranted in interpreting these results.

CONCLUSIONS

Cirrhosis results in high healthcare resource utilization, leading to high expenditures. On December 31, 2012, the prevalence in Catalonia was 459.9 per 100,000 inhabitants. The cost of treating cirrhotic patients was high because more than 75% had moderate to very high risk according to their GMA morbidity burden. The main expenditure was hospitalization; its weight in the total expenditure increased with decompensation.

Avoiding excessive alcohol consumption and eradicating hepatitis C infection with the new antiviral agents will probably modify the natural history of cirrhosis, reducing morbidity and mortality and consequently expenditures in these patients.

Contributor ship statement: All authors contribute in the concept and design , MC and EM acquisition of data and statistical analysis. MM, MV, MC and EM interpretation of data. MM and MV writing of the manuscript and all authors supervised and approved the manuscript.

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TABLE AND FIGURE LEGENDS:

Table 1: Demographic characteristics according toliver disease group

Table 2: Health services utilization in 2013 in function of liver disease group

Table 3: Multivariable logistic regression analyzing factors associated with expenditure higher than the 85th percentile

Figure 1: Health expenditure by type of resource in the general population and in cirrhotic patients, in millions of euros. The category “Other” includes mental health services, non-urgent medical transportation, outpatient rehabilitation, and homeoxygen therapy.

Figure 2: Healthcare resource use in cirrhotic patients by age.

Figure 3: Healthcare resource use in cirrhotic patients by hepatic decompensation.

Figure 4: Healthcare resource use in cirrhotic patients by risk stratification (morbidity burden).

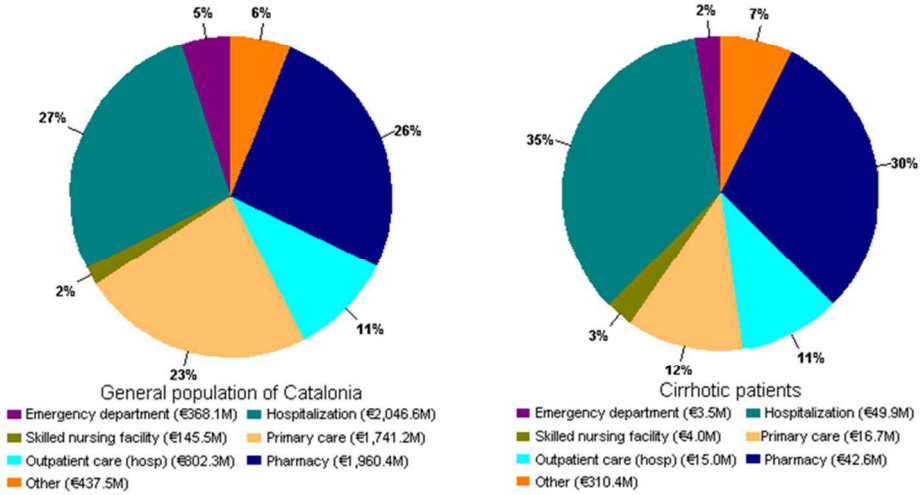
Supplement information

Appendix 1: Hepatic decompensation codes

Table1S: Mean price by activity

Table 2S: Demographic characteristics in function ofspecific hepatic decompensation during 2012

Table 3S: Health services utilization by specific hepatic decompensation during 2012



Health expenditure by type of resource in the general population and in cirrhotic patients, in millions of Euros. The category "Other" includes mental health services, non-urgent medical transportation, outpatient rehabilitation, and home oxygen therapy.

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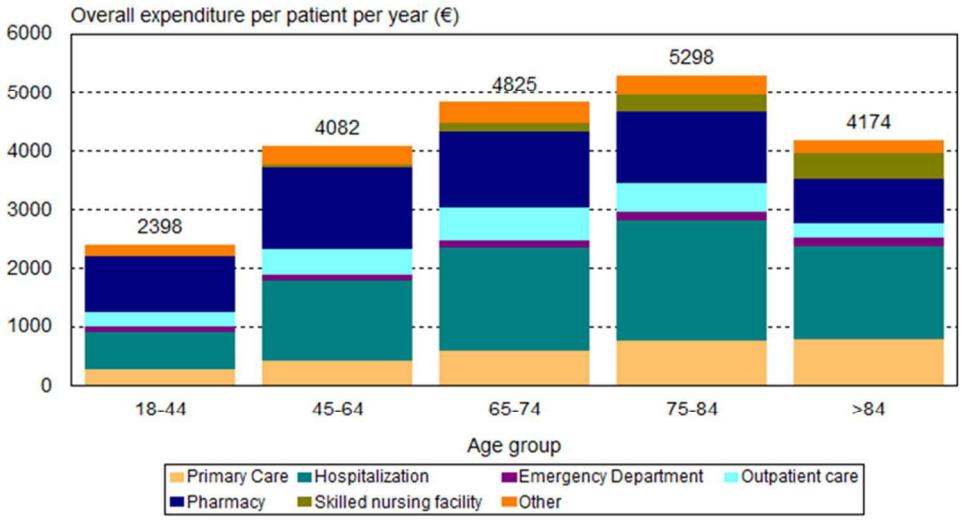

Healthcare resource use in cirrhotic patients by age.

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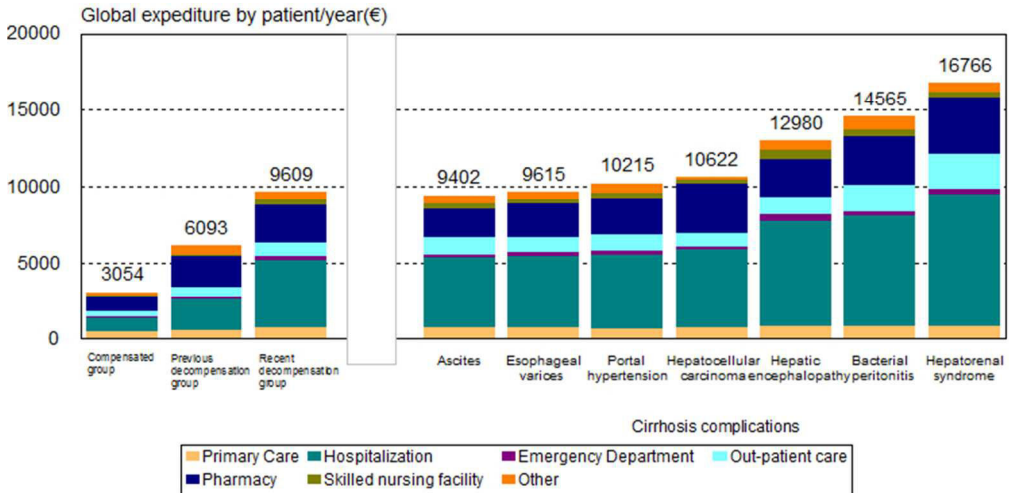

Healthcare resource use in cirrhotic patients by hepatic decompensation.

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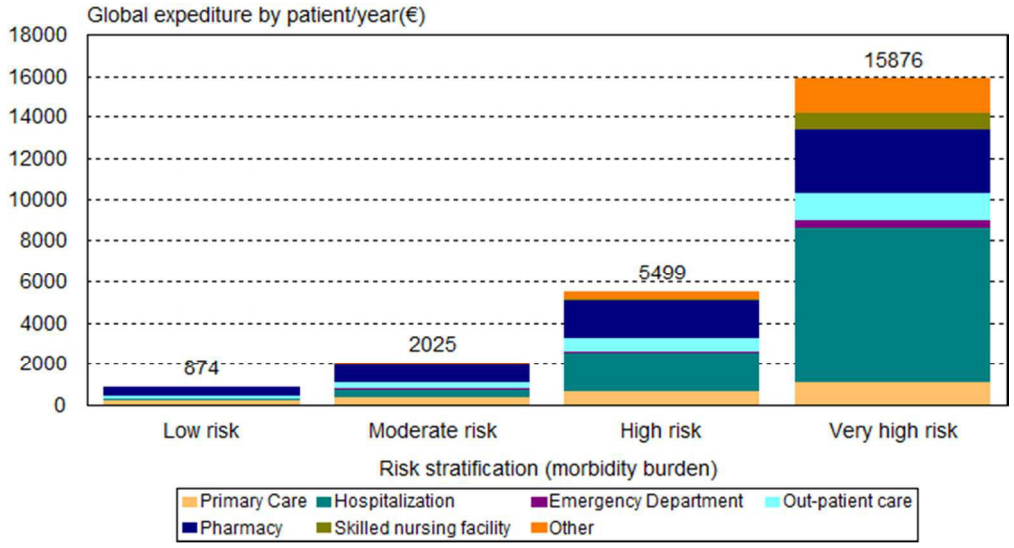

Healthcare resource use in cirrhotic patients by risk stratification (morbidity burden).

177x95mm (96 x 96 DPI)

Table 1: Demographic characteristics according to liver disease group

	TOTAL	Compensated group No hepatic decompensation	Hepatic decompensation	
			Previous decompensation group Decompensation before 2012, but not during 2012	**Recent decompensation group** Decompensation during 2012
Cases	34,740	25,299	5,393	4,048
Patients / year	33,567	24,737	5,195	3,635
Age mean±SD (years) *	61.2±13.9	60.6 ±14.4	62.2 ±12.6	63.7 ±12.7
Women (%)	41.7	44.8	33.8	33.4
Morbidity				
Number of chronic comorbidities (mean) *	5.1	4.7	6.0	6.5
Stratification group (AMG)*				
Very high-risk stratum (%)	11.6	7.8	17.0	27.8
High risk stratum (%)	30.6	26.0	41.0	45.4
Moderate risk stratum (%)	35.2	38.4	32.3	22.3
Low risk stratum (%)	22.2	27.8	9.7	4.5
Ischemic heart disease (%)*	12.1	10.6	15.3	17.4
Stroke (%)*	6.1	5.4	7.7	8.5
Heart failure (%)*	7.4	6.0	9.8	12.7
Diabetes (%)*	28.7	25.0	37.9	39.7
Renal failure (%)*	7.3	4.9	13.3	14.6
COPD (%)*	15.8	12.7	20.1	21.3
Dementia (%)	3.1	3.0	3.2	3.7
Depression (%)	22.3	22.2	22.3	23.2
Malignancy (%)*	19.0	13.5	27.9	41.3

Malnutrition (%)*	0.5	0.2	1.0	1.3
Anemia (%)*	21.3	12.1	42.5	50.7
HIV+ (%)*	2.6	1.7	5.1	5.0
Hepatitis C virus + (%)*	14.7	7.0	31.8	39.6
Alcohol (%)*	28.1	17.5	57.6	55.8
Drugs (%)*	4.2	3.0	7.5	7.5
Mortality and hepatic decompensation during 2013				
Mortality 2013 (%)*	6.7	4.3	8.5	19.4
Hepatic decompensation 2013 (%)*	11.7	2.7	21.3	54.8

AMG: Adjusted morbidity grouper; COPD: chronic obstructive pulmonary disease; HIV: human immunodeficiency virus.

* $p < 0.001$

Table 2: Health services utilization in 2013 in function of liver disease group

	Compensated group No hepatic decompensation	**Hepatic decompensation**	
		Previous decompensation group Decompensation before 2012, but not during 2012	**Recent decompensation group** Decompensation during 2012
Cases	25,299	5,393	4,048
Admission rate (x100)*	29.2	60.8	117.9
Mean length of hospitalization (days)*	1.8	4.5	9.6
Unplanned admission rate (x100)*	16.5	37.8	78.3
Patients with unplanned admission (%)*	10.8	22.9	40.3
Patients >1 unplanned admission (%)*	3.4	8.4	18.5
Emergency visit rates (x100)*	71.2	111.1	186.8
Patients with emergency visit (%)*	33.8	45.5	61.4
Patients with >1 emergency visits (%)*	15.7	25.7	38.8
Gastroenterology/hepatology specialist outpatient visits (average)*	0.6	1.8	2.6
Other hospital outpatient visits (average)	3.1	4.3	4.8
Primary care visits (average)*	11.8	13.4	16.5
Users of a skilled nursing facility (%)*	4.0	7.3	15.7
Mental health outpatient visits rate (x100)	16.6	13.5	15.1
Psychiatric hospital admission rate (x100)	.6	.7	1.6

* p< 0.001

Table 3: Multivariable logistic regression analyzing factors associated with expenditure higher than the 85th percentile

	n	β coefficient	OR	95% CI	
Sex					
Male	18,783		1	--	--
Female	13,631	-0.034	0.967	0.890	1.050
Age group					
18-44 years old	4,152		1	--	--
45-64 years old	15,027	0.037	1.037	0.881	1.222
65-74 years old	7,540	-0.154	0.858	0.720	1.022
75-84 years old	4,750	-0.515	0.597	0.496	0.720
>84 years old	945	-1.209	0.299	0.225	0.396
Hepatic decompensation					
Compensated group	24,219		1	--	--
Previous decompensation group	4,934	0.311	1.364	1.230	1.514
Recent decompensation group	3,261	0.687	1.988	1.770	2.234
Risk stratum (morbidity burden)					
Low risk stratum	7,694		1	--	--
Moderate risk stratum	12,202	1.126	3.082	2.454	3.870
High risk stratum	9,758	2.769	15.944	12.780	19.891
Very high risk stratum	2,760	4.850	127.704	100.533	162.218
Chronic kidney disease	2,075	0.113	1.120	0.988	1.269
Hepatitis C virus +	4,377	0.429	1.536	1.389	1.699
HIV+	823	2.930	18.734	15.374	22.828
Unplanned hospitalization during 2012					
0	27,687		1	--	--
1	3,208	0.117	1.124	0.992	1.274
2	944	0.168	1.183	0.974	1.437
3	326	0.461	1.586	1.176	2.139
>3	249	0.507	1.660	1.166	2.363
Emergency department visits during 2012					
0	20,034		1	--	--
1-2	8,919	0.190	1.209	1.095	1.334
3-5	2,648	0.415	1.514	1.314	1.743
>5	813	0.580	1.785	1.431	2.226
Skilled nursing facility during 2012	820	-0.339	0.713	0.587	0.865
Constant		-4.593	0.010	--	--

OR: Odds Ratio. **CI**: Confidence Interval. **HIV**: Human immunodeficiency virus

SUPPLEMENTARY MATERIAL:

Appendix 1: Hepatic decompensation codes:

- Encephalopathy: 572.2, 070.2, 070.4, 070.6, 070.71
- Portal hypertension: 572.3
- Hepatorenal syndrome: 572.4
- Spontaneous bacterial peritonitis: 032.83, 567.xx, 569.5
- Hepatocellular carcinoma: 155.0, 155.2, 197.7
- Ascites: 789.5
- Esophageal varices with or without bleeding: 456.0, 456.1, 456.2x

Table 1S: Mean price by activity

Primary care visits	
Physician	€ 38.04 per visit
Home visit (physician)	€ 45.65 per visit
Nurse	€ 22.83 per visit
Home visit (nurse)	€ 27.39 per visit
Specialist visit	€ 58.46 per visit
Mental health visit	€ 75.31 per visit
Emergency room visit	€ 106.38 per visit
Hospital admission	€ 2,150.64 per admission
Skilled nursing facility	
Long term	€ 50.22 per day
Convalescence	€ 86.91 per day

Mental health admission	
Acute	€ 183.31 per day
Sub-acute	€ 115.35 per day
Minor outpatient surgery	€ 156.84 per surgery
Outpatient Care Clinics	€ 169.35 per day
Hospital at home	€ 950.00 per admission
Outpatient rehabilitation	€ 213.39 per session
Non-urgent medical transportation	€ 61.34 per act
Home oxygen therapy	€ 49.12 per session
Dialysis	€ 151.20 per session

Table 2S: Demographic characteristics in function of specific hepatic decompensation during 2012

	TOTAL	Specific hepatic decompensation during 2012						
		EV	HE	SBP	HRS	CHC	ASC	PHT
Cases	4,048	1800	815	293	68	1006	786	1878
Patients / year	3,635	1613	664	252	49	852	689	1697
Age* (mean±SD) (years)	63.7 ±12.7	62.6 ±12.6	63.4 ±12.3	62.2 ±12.5	61.8 ±12.8	68.3 ±10.7	62.1 ±12.3	61.8 ±12.8
Women (%)	33.4	31.3	36.0	30.7	33.8	27.7	34.6	32.9
Morbidity								
Number of chronic co-morbidities		6.5	7.1	6.8	7.5	7.3	6.0	6.5
Stratification groups (AMG)								
Very high-risk stratum		27.9	40.9	36.9	44.1	28.0	26.8	29.1
High risk stratum		45.5	42.8	43.3	45.6	56.2	40.5	44.3
Moderate risk stratum		23.2	14.1	16.4	10.3	15.5	23.8	22.6
Low risk stratum		3.4	2.2	3.4	0.0	0.3	8.9	4.0

EV: Esophageal Varices; **HE**: Encephalopathy; **SBP**: Spontaneous bacterial peritonitis; **HRS**: Hepatorenal syndrome; **CHC**: Hepatocelular Carcinoma; **ASC**: Ascites. **PHT**: Portal Hypertension; AMG: Adjusted Morbidity Groups.

Table 3S: Health services utilization by specific hepatic decompensation during 2012

	Specific Hepatic decompensation during 2012						
	EV	**HE**	**SBP**	**HRS**	**CHC**	**ASC**	**PHT**
Cases	1800	815	293	68	1.006	786	1878
Admission rate (x100)	128.1	175.1	175.1	170.6	115.0	125.1	128.5
Average length of hospitalization (days)	10.8	15.1	17.7	13.6	7.3	10.6	10.9
Unplanned admission rate (x100)	87.8	131.0	112.6	97.1	58.7	88.5	87.0
Patients with unplanned admission (%)	42.2	55.1	51.2	52.9	35.6	45.0	43.3
Patients >1 unplanned admission (%)	20.7	30.8	28.3	23.5	13.5	21.0	20.9
Emergency visit rates (x100)	208.8	277.3	245.1	222.1	141.7	199.6	211.2
Patients with emergency visit (%)	63.7	70.1	69.3	63.2	57.0	61.5	65.0
Patients with >1 emergency visits (%)	40.9	48.5	50.2	36.8	33.9	40.7	41.8
Gastroenterology/hepatology specialist outpatient visits (mean	2.6	2.6	2.7	3.3	3.4	2.5	2.5
Other hospital outpatient visits (average)	4.6	4.2	6.0	3.8	4.5	4.6	5.2
Primary Care visits (average)	16.3	17.9	18.4	16.3	15.6	17.7	16.1
Users of a skilled nursing facility (%)	14.8	24.5	17.7	30.9	21.2	16.4	14.7
Mental Health outpatient visits rate (x100)	15.8	18.9	10.9	23.5	4.6	18.2	15.4
Psychiatric hospital admission rate (x100)	2.1	1.1	.7	2.9	.3	1.8	2.6

EV: Esophageal Varices; **HE**: Encephalopathy; **SBP**: Spontaneous bacterial peritonitis; **HRS**: Hepatorenal syndrome; **CHC**: Hepatocelular Carcinoma; **ASC**: Ascites. **PHT**: Portal Hypertension;

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ECONOMIC BURDEN OF CIRRHOSIS IN CATALONIA:A POPULATION- BASED ANALYSIS

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ECONOMIC BURDEN OF CIRRHOSIS IN CATALONIA: A POPULATION-BASED ANALYSIS

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List of Abbreviations:

ICD-9CM: Clinical Modification of the International Classification of Diseases, 9th Revision codes

DRG: Diagnosis-related group

AMG: Adjusted morbidity groups

ANOVA: Analysis of variance

CI: confidence interval

ABSTRACT

Background: Cirrhosis is a chronic disease with high morbidity and mortality. Few studies have evaluated healthcare resource use in patients with cirrhosis.

Objective: We aimed to describe the point prevalence of cirrhosis on December 31, 2012 and the population-level distribution of healthcare resource use and expenditures in a non-selected population of cirrhotic patients stratified by whether their disease was compensated or decompensated and by comorbidity burden.

Methods: This population study included all known patients aged >18 years with cirrhosis (according to ICD-9) in Catalonia, Spain, on December 31, 2012. We evaluated healthcare resource use and expenditure during 2013, taking into account the presence of decompensation before or during 2012.

Results: We documented 34,740 patients diagnosed with cirrhosis (58.7% men; mean age 61.8±14 years), yielding a point prevalence on December 31, 2012 of 460 per 100,000 inhabitants. Annual mortality was 9.1%. During 2013, healthcare expenditures on cirrhotic patients totaled €142.1 million (€4,234 per patient), representing 1.8% of the total 2013 healthcare budget of Catalonia. Hospitalization costs accounted for 35.1% of the total expenditure, and outpatient care accounted for 22.4%. Multivariable logistic regression identified morbidity burden, HIV infection, hospitalization, and emergency room visits during 2012 as independent predictors of expenditure > 85th percentile (area under the receiver operating curve, 0.88 (95%CI:0.883–0.893; P<0.001).

Conclusions: Cirrhosis accounts for a high proportion of healthcare resource usage and expenditures; hospitalization accounted for the greatest expenditures.

electronic count: 230

Strengths and limitations of this study:

- We perform a cost analysis using a population-based database including 34,740 patients diagnosed with cirrhosis in Catalonia, thus minimizing selection bias.
- The study quantified the total economic impact of cirrhosis in relation to the hepatic decompensation and determined the distribution of the costs involved in treating patients with this condition.
- We have not included important information such as the etiology of cirrhosis and other important clinical data for characterizing the study population and the evolution of the disease (i.e. MELD, Child-Pugh or ACLF).
- Using a validated risk assessment tool allowed us to calculate individuals' morbidity burden and to analyze the impact of multimorbidity on resource use and costs.
- Although the database is periodically monitored and has high quality data, using administrative data to identify cirrhotic patients can lead to misclassification.

INTRODUCTION:

Cirrhosis is a late stage in progressive liver disease of varying etiologies. The prevalence of cirrhosis among older adults is not well known, but is expected to increase, in part due to the rising incidence of nonalcoholic fatty liver disease and the aging of the hepatitis C population[1–3]. In fact, there is an increasing trend in the diagnosis of chronic liver disease and its decompensation and complications (including hepatocellular carcinoma)[4].

The interval between the compensated phase of cirrhosis and the development of complications (decompensated cirrhosis) is often long, with a reported median survival of 12 years[5,6]. Compared to age-matched patients without cirrhosis, patients with cirrhosis have worse health and more comorbid conditions, resulting in greater use of healthcare services, including more hospital visits, nursing home stays, and physician visits [2].

Chronic hepatitis C virus infection is one of the main causes of cirrhosis, and it is the most common indication for liver transplantation in Spain and worldwide[7,8]. Hepatitis C infection not only affects the liver, but is also associated with hypertension and other cardiovascular diseases, chronic renal impairment, and diabetes mellitus. Some studies have estimated the costs of hepatitis C infection without, however, analyzing the impact of complications of advanced liver disease [4].

Knowing the impact of decompensated disease on outcomes and on the cost of treating advanced liver disease is important for planning resource allocation and preventive strategies, especially in a public health system[8]. Because of its

importance in public health, a growing number of publications address chronic liver disease [2,8–11].

This study aimed to describe overall healthcare resource use and expenditures in a non-selected population of cirrhotic patients stratified into those with compensated disease and those with decompensated disease.

MATERIALS AND METHODS

Data Source and Study Design

We analyzed healthcare resource use and expenditures in 2013 in patients with cirrhosis residing in Catalonia, an autonomous region in Northeast Spain with 7,553,650 inhabitants (density, 232.8 inhabitants/km^2). The regional health department, named CatSalut, provides universal healthcare coverage to all residents and collects detailed information on healthcare usage, including information from the minimum basic dataset registered by healthcare units (e.g., hospitals, primary care centers, nursing facilities, and mental health centers). CatSalut also collects information on drug prescription and billing for services (e.g., outpatient visits to specialists, emergency department visits, non-urgent medical transportation, outpatient rehabilitation, home oxygen therapy, and dialysis). Initially, the Catalan health administration deployed a series of registers to record healthcare units' activity. In 2011, the Catalan Health Surveillance System (CHSS) was created to integrate most of those activity registers, placing the patient (instead of the provider) in the center of this information system, thus favoring longitudinal analysis and providing a more holistic and transversal view of health problems. The CHSS includes all the

diagnoses reported by the different providers, regardless of whether they were recorded as the primary or secondary diagnosis. This information system collects all information from the entire public health system, including all hospital admissions and healthcare visits. The CHSS contains 529 million diagnoses, 440 million contacts with the various public health services, and 519 million prescriptions dispensed by pharmacies. Its automated data validation system checks the consistency of the data and identifies potential errors. Moreover, as this information is used for healthcare provider payment purposes, periodic external audits are carried out to ensure the quality and reliability of the data.

Information from private health centers was not available for analysis, because although private hospitals notify CatSalut of their activity, they do not associate the reported data with each patient's identification number. Therefore, CatSalut has information about the activity performed, but not for individual patients. CatSalut administrative data showed that in 2013, of 2,878 unplanned hospitalizations of cirrhotic patients, 2,727 (94.8%) took place in public hospitals and only 151 (5.2%) in private hospitals.

Selection of Patients

This retrospective fixed cohort study included all residents of Catalonia aged 18 years or older diagnosed with cirrhosis on or before 31 December 2012 who were alive on that date. The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9CM) codes were used to identify cases with cirrhosis (Codes: 571.2 and 571.5) (see Suppinfo.Appendix1) as well as complications of cirrhosis.

We defined hepatic decompensation as an unscheduled hospital admission for hepatic encephalopathy, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, or hepatic complications such as hepatocellular carcinoma, esophageal varices, or portal hypertension. We divided patients into three groups:

- Compensated group: cirrhotic patients who had not had any episodes of hepatic decompensation before 2013,
- Previous decompensation group: patients who had had at least one episode of hepatic decompensation before 2012 but none during 2012,
- Recent decompensation group: patients who had at least one episode of hepatic decompensation during 2012.

Calculation of Expenditure

The primary outcome variable of the study was expenditures related to healthcare resource use in 2013. In Catalonia, expenditures for healthcare and pharmacy services are normally directly attributed to each patient through their personal health identification number. Expenditures for primary care are calculated indirectly from a standard price per visit weighted by attending professional (physician or nurse) and site of assistance. Expenditures for hospital care are weighted by diagnosis-related groups (DRG). Expenditures for in-patient care at hospitals, skilled nursing facilities, and mental health centers are calculated according to length of stay (supplement info: Table 1S shows the average price by activity in Catalonia). The costs are attributed to each person through their personal identification codes assigned by the public health system.

The prices used in the calculations are the rates that CatSalut pays healthcare providers, which are published annually in the Official Gazette of the Government of Catalonia.

CatSalut's budget for 2013 was €8,085 million, of which €7,885 million (97.5%) was devoted to healthcare services. Emergency medical transport and screening for breast and colon cancer accounted for the largest proportion of expenditures that were not individually allocated. The healthcare services in CatSalut's morbidity database accounted for €7,502 million (€968 per capita), which represents 95.1% of CatSalut's expenditure on health services.

In this population-based study, the methods used allowed us to analyze the expenditures on patients with cirrhosis, but not the costs attributable only to the disease itself. Thus, we calculated the total healthcare expenditure per person per year (in euros) for patients with cirrhosis (including cirrhosis-related care and care related to comorbidities), rather than the expenditure specifically associated with cirrhosis care. This approach enabled a comprehensive analysis of healthcare expenditures in this group of complex patients. To account for shorter follow-up periods due to deaths, time at risk was calculated in days from 31 December 2012 to the date of death (or 365 days otherwise) and transformed to years. Thus, the unit of analysis is not the patient but rather the patient/year.

Assessment of predictors of increased expenditure

We also sought to identify independent predictors associated with yearly expenditures greater than or equal to the 85th percentile of the distribution in the study population. This analysis included only patients who survived the

whole study period (n=32,414). Predictors assessed were age, sex, comorbidities included in the Charlson Index[12,13], previous healthcare utilization, and a novel population-based health risk assessment tool deployed in Catalonia, the Adjusted Morbidity Grouper (AMG), which is used to calculate an individual's morbidity burden [14]. The AMG categorizes each patient in a risk stratification pyramid with five strata:

- Basal risk stratum: comprising individuals with minimum morbidity burden; 50% of individuals in the overall population of Catalonia (but 0% of cirrhotic patients) fall into this stratum.
- Low risk stratum: comprising individuals with low level complexity; 30% of individuals in the overall population of Catalonia (but 22.2% of cirrhotic patients) fall into this stratum.
- Moderate risk stratum: comprising individuals with higher complexity than the previous risk stratum; 15% of individuals in the overall population of Catalonia (but 35.6% of cirrhotic patients) fall into this stratum.
- High risk stratum: comprising individuals with a greater morbidity burden than the previous stratum; 4% of individuals in the overall population of Catalonia (but 30.6% of cirrhotic patients) fall into this stratum.
- Very high-risk stratum: comprising individuals with the highest morbidity burden; 1% of individuals in the overall population of Catalonia (but 11.6% of cirrhotic patients) fall into this stratum.

Statistical analysis

Continuous variables are reported as means±standard deviations. For the univariate analysis, we used chi-square tests to compare categorical variables

and analysis of variance (ANOVA) to compare continuous variables. To identify independent predictors of increased healthcare expenditure, we used multivariable logistic regression. Variables were entered in the model one by one and retained when their significance was <0.10. To evaluate the discriminatory ability of the resulting predictive model for identifying cirrhotic patients with healthcare expenditures ≥85th percentile, we calculated the area under the receiver operating characteristic (ROC) curve[15]. Goodness of fit of the model was evaluated using the Homer-Lemeshow method. Statistical analyses were performed using SPSS software, version 18.0. All statistical tests and confidence intervals (CI) were constructed with a type I error level of 5%, and P-values <0.05 were considered significant.

Ethics

The study used retrospective data from administrative databases and patients were anonymous to the researchers. Our ethics committee stated that under Spanish legislation informed consent and ethics committee approval were not required.

RESULTS

Demographics of included patients

We documented 34,740 patients in Catalonia with cirrhosis on December 31, 2012 (460 per 100,000 inhabitants); of these 25,299 (72.8%) had never had any episodes of hepatic decompensation (Compensated group), 5,393 (15.5%) had had at least one episode of decompensation before 2012 (Previous decompensation group), and 4,048 (11.7%) had at least one episode of

decompensation during 2012 (Recent decompensation group). In the entire group, mean age was 61.2±14 years and 41.8% were women; however, the proportion of women decreased with worsening disease (44.8% in the Compensated group, 33.8% in the Previous decompensation group, and 33.4% in the Recent decompensation group) (p<0.001).

Patients with advanced liver disease had more comorbidities, and their comorbidities were more severe than those with less advanced disease. There were no significant differences in dementia or depression between groups. (Table 1; see also Table 2S)

Table 1: Demographic characteristics according to liver disease group

	TOTAL	Compensated group No hepatic decompensation	Hepatic decompensation	
			Previous decompensation group Decompensation before 2012, but not during 2012	Recent decompensation group Decompensation during 2012
Cases	34,740	25,299	5,393	4,048
Patients / year	33,567	24,737	5,195	3,635
Age mean±SD (years) *	61.2±13.9	60.6 ±14.4	62.2 ±12.6	63.7 ±12.7
Women (%)	41.7	44.8	33.8	33.4
Morbidity				
Number of chronic comorbidities (mean) *	5.1	4.7	6.0	6.5
Stratification group (AMG)*				
Very high-risk stratum (%)	11.6	7.8	17.0	27.8
High risk stratum (%)	30.6	26.0	41.0	45.4
Moderate risk stratum (%)	35.2	38.4	32.3	22.3
Low risk stratum (%)	22.2	27.8	9.7	4.5
Ischemic heart disease (%)*	12.1	10.6	15.3	17.4
Stroke (%)*	6.1	5.4	7.7	8.5
Heart failure (%)*	7.4	6.0	9.8	12.7

Diabetes (%)*	28.7	25.0	37.9	39.7
Renal failure (%)*	7.3	4.9	13.3	14.6
COPD (%)*	15.8	12.7	20.1	21.3
Dementia (%)	3.1	3.0	3.2	3.7
Depression (%)	22.3	22.2	22.3	23.2
Malignancy (%)*	19.0	13.5	27.9	41.3
Malnutrition (%)*	0.5	0.2	1.0	1.3
Anemia (%)*	21.3	12.1	42.5	50.7
HIV+ (%)*	2.6	1.7	5.1	5.0
Hepatitis C virus + (%)*	14.7	7.0	31.8	39.6
Alcohol (%)*	28.1	17.5	57.6	55.8
Drugs (%)*	4.2	3.0	7.5	7.5
Mortality and hepatic decompensation during 2013				
Mortality 2013 (%)*	6.7	4.3	8.5	19.4
Hepatic decompensation 2013 (%)*	11.7	2.7	21.3	54.8

AMG: Adjusted morbidity grouper; COPD: chronic obstructive pulmonary disease; HIV: human immunodeficiency virus. * p< 0.001

Hepatitis C infection was more common in patients who had episodes of decompensation, as was the use of sedatives and alcohol and/or drug abuse.

Overall mortality during 2013 was 6.7%. Mortality was 4.3% in the Compensated group, 8.5% in the Previous decompensation group, and 19.4% in the Recent decompensation group.

Table 3S (supplementary material) shows these patients' probability of dying, adjusted for different factors.

Use of Health Resources

The overall rate of hospitalizations was 44.4 per 100 patients; the rate increased with severity (29.2 in the Compensated group, 60.8 in the Previous

decompensation group, and 117.9 in the Recent decompensation group; p<0.0001) (Table 2). Table 4S (supplementary material) shows the probability of having at least one urgent hospital admission, adjusted by different factors.

Table 2: Health services utilization in 2013 in function of liver disease group

	Compensated group No hepatic decompensation	**Hepatic decompensation**	
		Previous decompensation group Decompensation before 2012, but not during 2012	**Recent decompensation group** Decompensation during 2012
Cases	25,299	5,393	4,048
Admission rate (x100)*	29.2	60.8	117.9
Mean length of hospitalization (days)*	1.8	4.5	9.6
Unplanned admission rate (x100)*	16.5	37.8	78.3
Patients with unplanned admission (%)*	10.8	22.9	40.3
Patients >1 unplanned admission (%)*	3.4	8.4	18.5
Emergency visit rates (x100)*	71.2	111.1	186.8
Patients with emergency visit (%)*	33.8	45.5	61.4
Patients with >1 emergency visits (%)*	15.7	25.7	38.8
Gastroenterology/hepatology specialist outpatient visits (average)*	0.6	1.8	2.6
Other hospital outpatient visits (average)	3.1	4.3	4.8
Primary care visits (average)*	11.8	13.4	16.5
Users of a skilled nursing facility (%)*	4.0	7.3	15.7
Mental health outpatient visits rate (x100)	16.6	13.5	15.1
Psychiatric hospital admission rate (x100)	.6	.7	1.6

* p< 0.001

Likewise, the mean length of hospitalization increased from 1.8 days in compensated patients to 4.5 days in previously decompensated patients to 9.6 days in recently decompensated patients.

The rate of hospital admissions from the emergency room in the entire group was 27 per 100 patients, being 16.5 in the Compensated group, 37.8 in the

Previous decompensation group, and 78.3 in the Recent decompensation group (p< 0.0001). Whereas 33.8% of the patients in the Compensated group presented at the emergency department at least once and 15.7% more than once, 45.5% of those in the Previous decompensation group presented at least once and 25.7% more than once, and 61.4% of those in the Recent decompensation group presented at least once and 38.8% more than once (Table 2, and table 5S).

Similarly, the number of gastroenterology outpatient visits significantly increased with hepatic decompensation. The number of outpatient visits to other departments also increased, but the difference did not reach statistical significance.

All patients had frequent contact with primary care physicians and/or nurses; the number of primary care visits increased with decompensation (11.8 in the Compensated group, 13.4 in the Previous decompensation group, and 16.5 in the Recent decompensation group; p<0.0001). The rate of outpatient visits to mental health centers and the rate of psychiatric hospitalization did not differ among groups. Moreover, the sicker patients were, the more they required social services from convalescence centers, intermediate- or long-stay centers, and palliative care centers

Assessment of healthcare expenditure

During 2013, a total of €142.1 million was spent in the care of cirrhotic patients in Catalonia (1.8% of the total 2013 healthcare budget), representing an average expenditure of €4,234 per patient/year.

Figure 1 displays the distribution of healthcare-related expenditures in cirrhotic patients and in the general population of Catalonia. In cirrhotic patients, the main source of expenditure was hospitalization (for all causes), which accounted for 35.1% of the total; pharmacy costs accounted for 30%, primary care for 11.8%, and hospital outpatient care for 10.6%. In contrast, in the general population the main source of expenses were hospitalization (27.3%), pharmacy (26.1%), primary care (23.2%), and hospital outpatient care (10.7%).

Figure 2 shows the distribution of healthcare-related expenditures in cirrhotic patients, stratified by age group. Despite some differences in resource use and expenditure among the different age groups, hospitalization accounted for the greatest expenditure in all groups.

Total medical expenditure was significantly higher for patients in the Recent decompensation group than for those in the Previous decompensation and compensated groups. In the Recent decompensation group, hospitalization was the main expenditure, accounting for more than half of all costs (Figure 3). By contrast, the total expenditure in the Compensated group was divided nearly equally among pharmacy, hospitalization, and outpatient care (hospital and primary care). The distribution of expenditures in the Previous decompensation group lay between those of the other two groups. Figure 3 also shows the distribution of expenditures in 2013 in patients in the Recent decompensation group according to the type of hepatic decompensation occurring in 2012; hepatorenal syndrome, followed by spontaneous bacterial peritonitis and

hepatic encephalopathy, generated much higher expenditures than other complications, mainly due to hospitalization.

In cirrhotic patients, the average healthcare expenditure increased with the number of chronic comorbidities, from €773/year in patients with one comorbidity to €14,853/year in those with >9 comorbidities. The AMG stratum was higher in patients with more comorbidities, and expenditures increased exponentially with increasing AMG strata, from less than €900 for patients in the low risk stratum to more than €15,000 for those in the very high risk stratum (Figure 4).

In patients with lower healthcare resource use (with expenditures < 85th percentile), expenditures were nearly equally distributed among primary care, pharmacy, and hospitalization. In patients with the highest healthcare resource use (expenditures ≥ 85th percentile), hospitalization accounted for nearly half of all expenditures; total healthcare expenditure in this group was ten times higher (€17,822 vs €1,806 patient/year) than in patients with lower resource use.

Table 3 reports the multivariable logistic regression analysis to identify predictors of high expenditure. Morbidity burden (AMG stratum), HIV infection, hospitalization, and emergency room visits during 2012 were associated with expenditures greater than or equal to the 85th percentile (i.e., > €7,275 per patient). The area under the ROC curve for identifying patients with expenditures greater than or equal to 85th percentile was 0.888 (95% CI: 0.883–0.893, Hosmer-Lemeshow test: X2: 29.997 (p<0.001)) . These results

show that the model identifies which patients will have higher health expenditures.

Table 3: Multivariable logistic regression analyzing factors associated with expenditure higher than the 85th percentile

	n	β coefficient	OR	95% CI	
Sex					
Male	18,783		1	--	--
Female	13,631	-0.034	0.967	0.890	1.050
Age group					
18-44 years old	4,152		1	--	--
45-64 years old	15,027	0.037	1.037	0.881	1.222
65-74 years old	7,540	-0.154	0.858	0.720	1.022
75-84 years old	4,750	-0.515	0.597	0.496	0.720
>84 years old	945	-1.209	0.299	0.225	0.396
Hepatic decompensation					
Compensated group	24,219		1	--	--
Previous decompensation group	4,934	0.311	1.364	1.230	1.514
Recent decompensation group	3,261	0.687	1.988	1.770	2.234
Risk stratum (morbidity burden)					
Low risk stratum	7,694		1	--	--
Moderate risk stratum	12,202	1.126	3.082	2.454	3.870
High risk stratum	9,758	2.769	15.944	12.780	19.891
Very high risk stratum	2,760	4.850	127.704	100.533	162.218
Chronic kidney disease	2,075	0.113	1.120	0.988	1.269
Hepatitis C virus +	4,377	0.429	1.536	1.389	1.699
HIV+	823	2.930	18.734	15.374	22.828
Unplanned hospitalization during 2012					
0	27,687		1	--	--
1	3,208	0.117	1.124	0.992	1.274
2	944	0.168	1.183	0.974	1.437
3	326	0.461	1.586	1.176	2.139
>3	249	0.507	1.660	1.166	2.363
Emergency department visits during 2012					
0	20,034		1	--	--
1-2	8,919	0.190	1.209	1.095	1.334
3-5	2,648	0.415	1.514	1.314	1.743
>5	813	0.580	1.785	1.431	2.226
Skilled nursing facility during 2012	820	-0.339	0.713	0.587	0.865
Constant		-4.593	0.010	--	--

OR: Odds Ratio. **CI**: Confidence Interval. **HIV**: Human immunodeficiency virus

DISCUSSION

In our study, liver cirrhosis had an important impact on healthcare expenditures, and hospitalization and pharmacy accounted for the largest proportion of costs associated with treating cirrhotic patients. To our knowledge, this is the first population-based study to quantify the total economic impact of cirrhosis in relation to hepatic decompensation and to determine the distribution of costs (including those related with primary, nursing, hospital, and mental health care as well as physical therapy and pharmacy) in treating patients with this condition.

This population-based study conducted in Catalonia included around 7,500,000 million people, which is comparable to the population of some European countries.

In recent years, many studies have estimated the economic burden of hepatitis and cirrhosis[16] because these conditions are associated with high morbidity, mortality, and economic costs. Although one of these analyzed the cost of care over the last year of life in patients with an end-stage liver disease [17], it was not a population-based study like ours. Another study described the direct costs related to hospital admissions in patients with cirrhosis [10]. By contrast, our study included all healthcare-related expenses in patients with cirrhosis (during hospitalization and afterwards). Another study analyzed both direct and indirect costs of chronic liver disease, but included all patients, not only those with cirrhosis [18].

Liver cirrhosis leads to 800,000 deaths every year, representing 1.3% of all deaths worldwide. According to the World Health Organization, cirrhosis is

among the eighteen most common causes of death[11]. Five-year survival is 36% in alcoholic cirrhosis and 14% in nonalcoholic cirrhosis [11]. We found that mortality increased significantly in patients who had a recent hepatic decompensation, and the risk of mortality increased nearly 20% in patients with a decompensation in the previous 12 months.

The total cost of treating cirrhotic patients in Catalonia in 2013 was almost €150 million (€4,234 per patient). Hospitalization remains the main source of healthcare-related expenditure, followed by medication, although hospital mortality has decreased in recent years[16]. Patients with more advanced liver disease required more healthcare (more days hospitalized, emergency visits, and primary care visits) and more medication, generating greater expenditures. In patients with cirrhosis, the probability of dying within a year of a hepatic decompensation is 34%[19]. In our study, mortality was nearly 2.3 times higher in patients with a recent decompensation than in patients who had gone at least a year since a prior decompensation and 4.5 times higher than those who had never had a decompensation. Our model's ability to differentiate patients who will require high expenditures suggests that our study can be useful in health planning, resource allocation, and evaluation of results.

Our large database allowed us to calculate the morbidity burden using the AMG[20] and to stratify the risk of morbimortality. In our population, morbidities were common, and greater severity of liver disease was associated with higher morbidity burden (>75% of all patients were in moderate or higher risk strata: 72.2% in the Compensated group, 90.3% in the Previous decompensation

group, and 95.5% in the Recent decompensation group). Moreover, expenditures increased with increasing AMG strata, so controlling comorbidities is one way to reduce costs.

Another way to reduce costs is to modify the natural history of the liver disease. Studies that have analyzed the direct and indirect costs of treating hepatitis C infection point out that costs rise with the natural history of the disease [17,21,22]. New antiviral agents against hepatitis C have modified the natural history of the disease, but the impact of these agents on the overall cost of treating patients with hepatitis C infection will not become clear until a few years have passed [23]. Nevertheless, our results suggest that this impact is likely to be significant because expenditures in patients with recent hepatic decompensation totaled more than twice those in patients who had not had a decompensation for at least one year and more than 3 times those in patients with compensated cirrhosis.

Although some studies have analyzed the costs of caring for other diseases such as diabetes mellitus [24] or heart failure [20], to our knowledge, this is the first population-based study to analyze morbidity and costs in patients with liver disease taking into account hepatic decompensation. Although several studies have evaluated some aspects involved in caring for cirrhotic patients (hospitalization, care giving hours) [2], our study analyzed overall costs, including expenditures on nursing, primary care, and mental health.

Limitations: The use of a general population database minimized selection bias and allowed us to analyze a real-world population. However, using administrative data to identify cirrhotic patients can lead to misclassification,

especially in patients diagnosed in private centers who have not used public resources.

Moreover, this administrative database did not include important information such as the etiology of cirrhosis (although alcohol consumption and/or hepatitis C infection are recorded in the database) or other important clinical data for characterizing and understanding the study population and the evolution of the disease. For these reasons, we cannot calculate classical scores such as MELD, Child-Pugh, or ACLF.

Patients' need for social services increases when liver disease becomes decompensated. The costs associated with this increase are, however, difficult to quantify and vary widely among health systems. Although these data are provided in the supplementary data, caution is warranted in interpreting these results.

Finally, we excluded patients who died during 2013 from the analysis of risk factors, although they were included in the analysis of healthcare expenditures. The reason for this exclusion is that patients who died during the study period were excluded from the assessment of predictors of increased expenditure. Although this exclusion could lead to bias, the cost of these patients after their death was zero. Therefore, the inclusion of dead patients in the analysis could lead to a possible bias in the calculation of the odd ratios of risk factors and consequently to errors in interpretation when diseases with high mortality are analyzed. Among the possible solutions for this bias, we opted for the simplest solution, and we analyzed only patients who remained alive throughout the year. This strategy has two main advantages: simplicity and robustness. In contrast to similar strategies, each of which introduces some sort of bias, we

believe it is better to use the simplest and easiest strategy to explain and understand the data. Moreover, one of the strengths of our study is that as it is a population-based study with real data, there is no need for methodological sophistication when a simpler strategy can be used.

CONCLUSIONS

Cirrhosis results in high healthcare resource utilization, leading to high expenditures. On December 31, 2012, the point prevalence in Catalonia was 459.9 per 100,000 inhabitants. The cost of treating cirrhotic patients was high because more than 75% had moderate to very high risk according to their AMG morbidity burden. The main expenditure was hospitalization; its weight in the total expenditure increased with decompensation.

Avoiding excessive alcohol consumption and eradicating hepatitis C infection with the new antiviral agents will probably modify the natural history of cirrhosis, reducing morbidity and mortality and consequently expenditures in these patients.

Contributor ship statement: All authors have contributed in the concept and design, Montserrat Clèries (MC) and Emili Vela (EV) in data acquisition and statistical analysis, Mireia Miquel (MM), Mercedes Vergara (MV), MC, and EV in interpretation of data, and MM and MV in writing the manuscript. All authors have supervised and approved the manuscript.

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TABLE AND FIGURE LEGENDS:

Table 1: Demographic characteristics according to liver disease group

Table 2: Health services utilization in 2013 stratified by liver disease group

Table 3: Multivariable logistic regression analyzing factors associated with expenditure higher than the 85th percentile

Figure 1: Health expenditure by type of resource in the general population and in cirrhotic patients, in millions of euros. The category “Other” includes mental health services, non-urgent medical transportation, outpatient rehabilitation, and home oxygen therapy.

Figure 2: Healthcare resource use in cirrhotic patients by age.

Figure 3: Healthcare resource use in cirrhotic patients by hepatic decompensation.

Figure 4: Healthcare resource use in cirrhotic patients by risk stratification (morbidity burden).

Supplementary information

Appendix 1: Hepatic decompensation codes

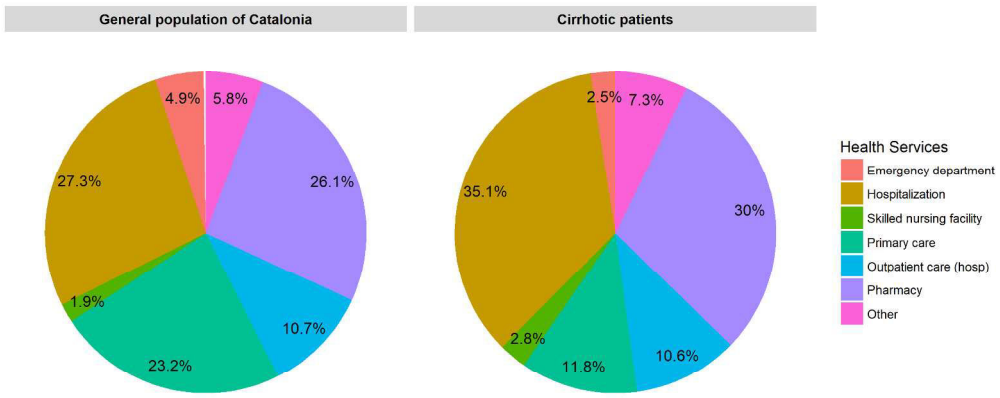
Table1S: Mean price by activity

Table 2S: Demographic characteristics stratified by specific hepatic decompensation during 2012

Table 3S: Probability of these patients dying, adjusted for different factors

Table 4S: Multivariable logistic regression analyzing factors associated with any hospitalization cause

Table 5S: Health services utilization by specific hepatic decompensation during 2012



Health expenditure by type of resource in the general population and in cirrhotic patients, in millions of euros.

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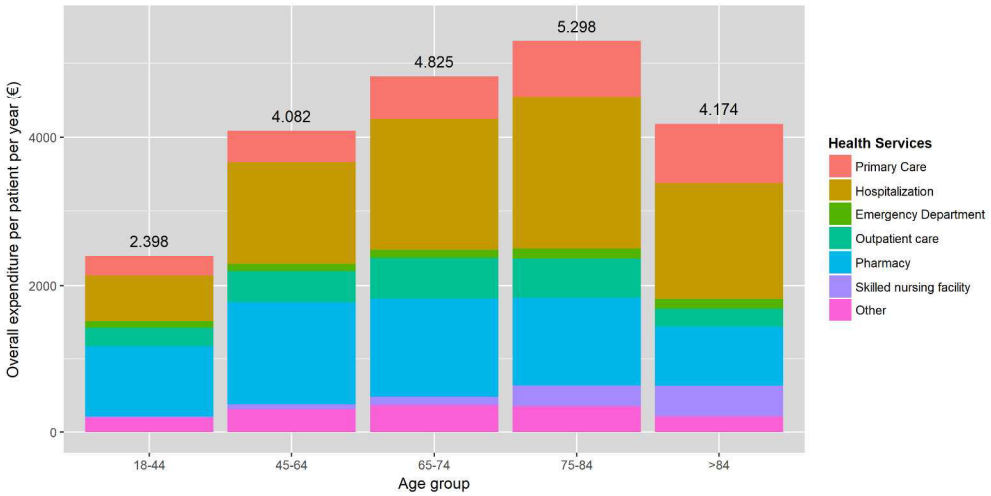
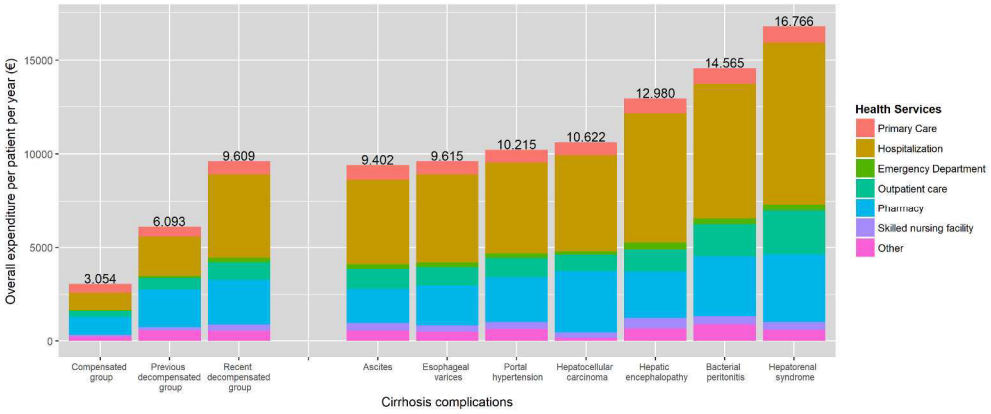


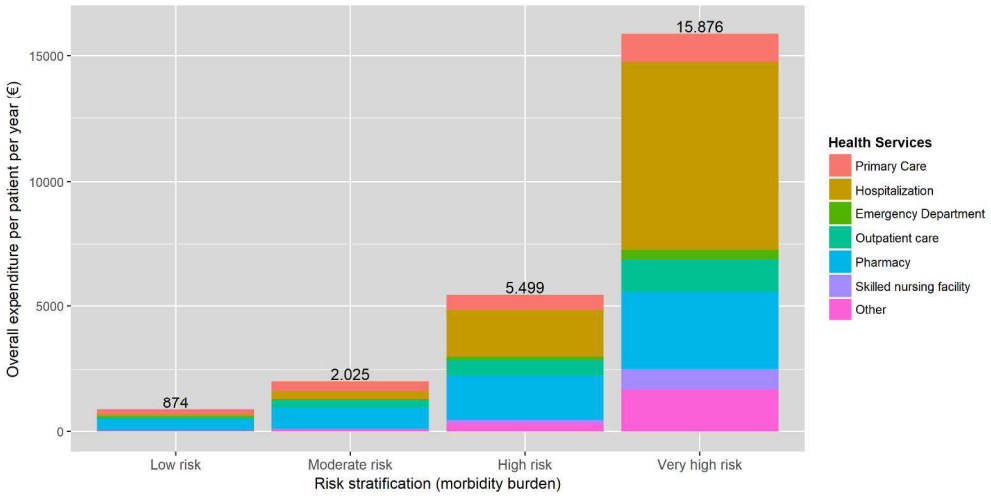
Healthcare resource use in cirrhotic patients by age

253x126mm (300 x 300 DPI)



Healthcare resource use in cirrhotic patients by hepatic decompensation.

304x126mm (300 x 300 DPI)



Healthcare resource use in cirrhotic patients by risk stratification (morbidity burden).

253x126mm (300 x 300 DPI)

SUPPLEMENTARY MATERIAL:

Appendix 1: Hepatic decompensation codes:

- Encephalopathy: 572.2, 070.2, 070.4, 070.6, 070.71
- Portal hypertension: 572.3
- Hepatorenal syndrome: 572.4
- Spontaneous bacterial peritonitis: 032.83, 567.xx, 569.5
- Hepatocellular carcinoma: 155.0, 155.2, 197.7
- Ascites: 789.5
- Esophageal varices with or without bleeding: 456.0, 456.1, 456.2x

Table 1S: Mean price by activity

Primary care visits	
Physician	€ 38.04 per visit
Home visit (physician)	€ 45.65 per visit
Nurse	€ 22.83 per visit
Home visit (nurse)	€ 27.39 per visit
Specialist visit	€ 58.46 per visit
Mental health visit	€ 75.31 per visit
Emergency room visit	€ 106.38 per visit
Hospital admission	€ 2,150.64 per admission
Skilled nursing facility	
Long term	€ 50.22 per day
Convalescence	€ 86.91 per day

Mental health admission	
Acute	€ 183.31 per day
Sub-acute	€ 115.35 per day
Minor outpatient surgery	€ 156.84 per surgery
Outpatient Care Clinics	€ 169.35 per day
Hospital at home	€ 950.00 per admission
Outpatient rehabilitation	€ 213.39 per session
Non-urgent medical transportation	€ 61.34 per act
Home oxygen therapy	€ 49.12 per session
Dialysis	€ 151.20 per session

Table 2S: Demographic characteristics stratified by specific hepatic decompensation during 2012

	TOTAL	Specific hepatic decompensation during 2012						
		EV	HE	SBP	HRS	CHC	ASC	PHT
Cases	4,048	1800	815	293	68	1006	786	1878
Patients / year	3,635	1613	664	252	49	852	689	1697
Age* (mean±SD) (years)	63.7 ±12.7	62.6 ±12.6	63.4 ±12.3	62.2 ±12.5	61.8 ±12.8	68.3 ±10.7	62.1 ±12.3	61.8 ±12.8
Women (%)	33.4	31.3	36.0	30.7	33.8	27.7	34.6	32.9
Morbidity								
Number of chronic co-morbidities		6.5	7.1	6.8	7.5	7.3	6.0	6.5
Stratification groups (AMG)								
Very high-risk stratum		27.9	40.9	36.9	44.1	28.0	26.8	29.1
High risk stratum		45.5	42.8	43.3	45.6	56.2	40.5	44.3
Moderate risk stratum		23.2	14.1	16.4	10.3	15.5	23.8	22.6
Low risk stratum		3.4	2.2	3.4	0.0	0.3	8.9	4.0

EV: Esophageal Varices; **HE**: Encephalopathy; **SBP**: Spontaneous bacterial peritonitis; **HRS**: Hepatorenal syndrome; **CHC**: Hepatocellular carcinoma; **ASC**: Ascites. **PHT**: Portal Hypertension; AMG: Adjusted Morbidity Groups.

Table 3S: Multivariable logistic regression analyzing factors associated with mortality

	n	β coefficient	OR	95% CI	
Sex					
Male	20,231		1	--	--
Female	14,509	-0.318	0.727	0.658	0.804
Age group					
18-44 years old	4,214		1	--	--
45-64 years old	15,671	0.338	1.402	1.058	1.857
65-74 years old	8,132	1.849	1.386	2.465	1.849
75-84 years old	5,497	2.761	2.069	3.684	2.761
>84 years old	1,226	5.992	4.368	8.220	5.992
Hepatic decompensation					
Compensated group	25,299		1	--	--
Previous decompensation group	5,393	0.314	1.369	1.202	1.558
Recent decompensation group	4,048	2.030	1.792	2.299	2.030
Risk stratum (morbidity burden)					
Low risk stratum	7,724		1	--	--
Moderate risk stratum	12,367	0.951	2.588	1.747	3.835
High risk stratum	10,622	11.348	7.805	16.500	11.348
Very high risk stratum	4,027	42.673	29.180	62.403	42.673
Chronic kidney disease	2,542	0.790	0.694	0.899	0.790
Hepatitis C virus +	5,096	1.213	1.081	1.360	1.213
HIV+	903	0.973	0.743	1.274	0.973
Unplanned hospitalization during 2012					
0	28,884		1	--	--
1	3,788	0.224	1.251	1.086	1.440
2	1,207	1.201	0.987	1.461	1.201
3	459	1.150	0.879	1.504	1.150
>3	402	1.560	1.166	2.088	1.560
Emergency department visits during 2012					
0	20,699		1	--	--
1-2	9,712	0.073	1.076	0.945	1.225
3-5	3,237	1.497	1.271	1.762	1.497
>5	1,092	1.576	1.253	1.982	1.576
Skilled nursing facility during 2012	1,234	2.127	1.832	2.470	2.127
Constant		0.003	0.003	--	--

Table 4S: Multivariable logistic regression analyzing factors associated with hospitalization for any cause

	n	β coefficient	OR	95% CI	
Sex					
Male	20,231		1	--	--
Female	14,509	-0.009	0.991	0.918	1.069
Age group					
18-44 years old	4,214		1	--	--
45-64 years old	15,671	-0.369	0.691	0.590	0.810
65-74 years old	8,132	-0.540	0.583	0.493	0.689
75-84 years old	5,497	-0.476	0.621	0.523	0.738
>84 years old	1,226	-0.315	0.730	0.587	0.907
Hepatic decompensation					
Compensated group	25,299		1	--	--
Previous decompensation group	5,393	0.405	1.499	1.362	1.650
Recent decompensation group	4,048	0.714	2.041	1.840	2.265
Risk stratum (morbidity burden)					
Low risk stratum	7,724		1	--	--
Moderate risk stratum	12,367	1.609	4.997	3.653	6.837
High risk stratum	10,622	3.759	42.917	31.679	58.141
Very high risk stratum	4,027	5.879	357.497	261.233	489.235
Chronic kidney disease	2,542	-0.549	0.578	0.515	0.647
Hepatitis C virus +	5,096	-0.021	0.980	0.891	1.077
HIV+	903	-0.100	0.904	0.741	1.104
Unplanned hospitalization during 2012					
0	28,884		1	--	--
1	3,788	0.296	1.344	1.203	1.503
2	1,207	0.402	1.494	1.264	1.767
3	459	0.399	1.490	1.159	1.915
>3	402	0.569	1.766	1.322	2.358
Emergency department visits during 2012					
0	20,699		1	--	--
1-2	9,712	0.185	1.204	1.098	1.320
3-5	3,237	0.403	1.496	1.319	1.698
>5	1,092	0.572	1.773	1.462	2.149
Skilled nursing facility during 2012	1,234	-0.437	0.646	0.555	0.751
Constant		-4.988	0.007	--	--

Table 5S: Health services utilization by specific hepatic decompensation during 2012

	Specific hepatic decompensation during 2012						
	EV	**HE**	**SBP**	**HRS**	**CHC**	**ASC**	**PHT**
Cases	1800	815	293	68	1.006	786	1878
Admission rate (x100 patients)	128.1	175.1	175.1	170.6	115.0	125.1	128.5
Average length of hospitalization (days)	10.8	15.1	17.7	13.6	7.3	10.6	10.9
Unplanned admission rate (x100 patients)	87.8	131.0	112.6	97.1	58.7	88.5	87.0
Patients with unplanned admission (%)	42.2	55.1	51.2	52.9	35.6	45.0	43.3
Patients >1 unplanned admission (%)	20.7	30.8	28.3	23.5	13.5	21.0	20.9
Emergency visit rates (x100 patients)	208.8	277.3	245.1	222.1	141.7	199.6	211.2
Patients with emergency visit (%)	63.7	70.1	69.3	63.2	57.0	61.5	65.0
Patients with >1 emergency visits (%)	40.9	48.5	50.2	36.8	33.9	40.7	41.8
Gastroenterology/hepatology specialist outpatient visits (mean	2.6	2.6	2.7	3.3	3.4	2.5	2.5
Other hospital outpatient visits (average)	4.6	4.2	6.0	3.8	4.5	4.6	5.2
Primary Care visits (average)	16.3	17.9	18.4	16.3	15.6	17.7	16.1
Users of a skilled nursing facility (%)	14.8	24.5	17.7	30.9	21.2	16.4	14.7
Mental Health outpatient visits rate (x100 patients)	15.8	18.9	10.9	23.5	4.6	18.2	15.4
Psychiatric hospital admission rate (x100 patients)	2.1	1.1	.7	2.9	.3	1.8	2.6

EV: Esophageal varices; **HE**: Encephalopathy; **SBP**: Spontaneous bacterial peritonitis; **HRS**: Hepatorenal syndrome; **CHC**: Hepatocellular carcinoma; **ASC**: Ascites. **PHT**: Portal hypertension;