Disease severity predicts higher healthcare costs among hospitalized nonalcoholic fatty liver disease/nonalcoholic steatohepatitis (NAFLD/NASH) patients in Spain

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Abstract (250; structured; max 250 words)

Objective: The rising prevalence of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) presents many public health challenges, including a substantial impact on healthcare resource utilization and costs. There are important regional differences in the burden of NAFLD/NASH, and Spain-specific data are lacking. This retrospective, observational study examined the impact of liver disease severity, comorbidities, and demographics on healthcare resource utilization and costs in Spain.

Methods: Patients enrolled in Spanish National Health System's Hospital Discharge Records Database were categorized as incident NAFLD/NASH, NAFLD/NASH non-progressors, compensated cirrhosis (CC), decompensated cirrhosis (DCC), liver transplantation (LT), or hepatocellular carcinoma (HCC). Patients were followed for a 6-month post-index period for liver disease progression. Pre- and post-index healthcare resource utilization and costs per patient per month (PPPM) in 2017 Euro were calculated.

Results: A total of 8,205 NAFLD/NASH patients (mean age 58.4; 54% males) were identified; 5,984 (72.9%) were non-progressors, 2,028 (24.7%) progressed to DCC, 139 (1.7%) to CC, 115 (1.4%) to LT, and 61 (0.7%) to HCC. Pre-index comorbidity burden was high across cohorts, and the frequency of comorbidities increased with disease severity. Average length of stay (LOS) increased significantly (23% to 41%) from pre- to post-index, with significantly longer LOS in patients with more severe liver disease. All-cause PPPM costs increased significantly (44% to 46%) from pre- to post-index, with higher costs evident for more severe disease.

Conclusions: Progression of NAFLD/NASH was associated with significantly higher costs and longer LOS. A coordinated approach is needed to manage resources and costs in Spain.

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a leading cause of chronic liver disease worldwide,[1-5] with disease severity ranging from simple steatosis to the combination of steatosis, inflammation, and hepatocyte ballooning that is characteristic of nonalcoholic steatohepatitis (NASH).[6,7] NAFLD/NASH is widely recognized as the hepatic manifestation of metabolic syndrome,[6,8,9] and affected patients at increased risk of insulin resistance and type 2 diabetes mellitus,[7,10-13] hyperlipidemia,[7,12-14] obesity,[13,15,16] and hypertension.[7,12,13,15,17] With the progression of NAFLD to NASH, patients are also at substantially greater risk of liver fibrosis and cirrhosis,[7,13,15,18] hepatocellular carcinoma (HCC),[4,7,13,15,18,19] liver transplantation (LT),[20,21] and death.[7,13,22,23]

The prevalence of NAFLD/NASH is projected to increase worldwide as obesity and diabetes rates continue to rise and the population of the world ages, with current estimates suggesting that 25% of the global adult population has NAFLD, and 3% to 5% are affected by NASH.[3,24] A dynamic Markov model, based on data from national reports and surveillance activities combined with a literature review and consultation with experts, characterized trends in NAFLD prevalence and progression in eight countries including China, France, Germany, Italy, Japan, Spain, the United Kingdom (UK), and the United States (US). By 2030, the NAFLD population is projected to increase worldwide by 18.3% to 100.9 million cases, with a 15% to 56% increase in the worldwide prevalence of NASH. Within Europe, the highest prevalence of NAFLD is predicted for Italy at 29.5%, and the highest prevalence of NASH is estimated for Spain at 29.5%.[1]

As the prevalence of NAFLD and NASH rises, the associated health, economic, and personal impacts on patients, family members, society, and healthcare delivery systems are expected to

increase substantially.[5,25-28] NALFD/NASH has a significant and negative impact on patients' quality of life and wellbeing.[28-32] Affected patients also experience higher rates of depression than patients with hepatitis B and the general population,[33] and are at increased lifetime risk of major depressive disorder.[34]

NAFLD/NASH also imposes a substantial burden on healthcare resource utilization and costs.[5,26,27,35,36] Annual direct medical costs for all incident and prevalent cases of NAFLD were estimated at €35 billion in 2016 for Germany, France, Italy, and the UK, with societal costs ranging from €31 billion in the UK to €75.7 billion in France.[27] Healthcare resource utilization and costs are significantly higher for patients who progress to more severe liver disease compared with NAFLD/NASH and no progression.[25,37] The impact of NAFLD/NASH on healthcare systems and direct costs is projected to increase[5,36] as the number of affected persons rises in Europe and worldwide.

Accurate estimates of the prevalence and burden of NAFLD/NASH are required for the design, implementation, and evaluation of a strategic public health response to address the growing impact of NAFLD/NASH in specific countries and regions of the world.[5,38,39] It is well-recognized that the burden of NAFLD/NASH is diverse, with variations in the epidemiology of disease as well as risk factors associated with disease development and progression.[39] Modeling approaches provide useful information about variations between countries and regions, but are subject to a number of limitations including inconsistencies in clinical assessment of steatosis, variability in case definitions, incomplete data, use of older data that may not accurately represent current patterns and trends, differences in diagnostic and staging techniques, and small sample sizes.[1,7] Real-world, population-based data can more accurately characterize the prevalence,

progression, and economic impact of NAFLD and NASH within specific countries and regions, which, in turn, can inform health policy.[40] A cross-sectional study reported an overall prevalence for NAFLD of 25.8% in adult patients receiving treatment at primary care centers in Catalonia, Spain, ranging from 20.3% in women to 33.4% in men. [Caballería 2010] Important limitations of this study were a 60% nonparticipation rate and reliance on echography for the diagnosis of NAFLD.

We performed this study to characterize the current prevalence of NAFLD/NASH and identify factors associated with disease progression and health care burden in NAFLD/NASH patients with and without advanced liver disease in Spain. The specific study objectives were to evaluate the impact of severity of liver disease, demographic characteristics, and comorbid health conditions on healthcare resource utilization and costs in a large real-world cohort of NAFLD/NASH patients in Spain.

Methods

Design and data source

We performed a longitudinal, retrospective cohort study using data from Spanish National Health System's Hospital Discharge Records Database (Conjunto Mínimo Básico de Datos or CMBD) for the period 01 January 2006 through 30 April 2017. Under the supervision of the Spanish Ministry of Health, the CMBD compiles information from 192 private and 313 public hospitals in all regions of Spain. The database contains patient-level information on demographic characteristics, primary and secondary diagnoses, readmissions, health care costs, dates of admission and

discharge, and mean length of stay for hospitalized patients. Information for this study was available for more than 36 million patients between 2006 and 2017.

Patient-level data were anonymized in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. According to Spanish data protection regulations, patient consent and approval by an institutional review board or ethics committee were not required for de-identified patient information.

Sample selection

Patients eligible for inclusion in this analysis were ≥18 years with at least one inpatient claim between January 1, 2006 and April 30, 2017 for a known diagnosis of NAFLD or NASH. A diagnosis of NAFLD or NASH was based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 571.8 and 571.9 and the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes K76.0, K75.81. ICD-10-CM codes were first implemented in Spain in January 2016, and this study includes a time period that preceded and followed the implementation of ICD-10-CM codes. Therefore, both ICD-9-CM and ICD-10-CM diagnosis codes for NAFLD and NASH were utilized.

Patients were excluded if, at any time during the study period, they were diagnosed with HIV, viral hepatitis B or C, autoimmune hepatitis, any other viral hepatitis, personal history of alcoholism, alcohol dependence, alcoholic liver diseases, toxic liver disease, Wilson's disease, Gaucher's disease, lysosomal acid lipase deficiency, biliary cirrhosis, cholangitis, and hemochromatosis. The complete list of ICD-9-CM and ICD-10-CM codes for NAFLD/NASH, CC, DCC, LT and HCC are contained in Appendix A.

Study cohorts

Eligible patients were required to have continuous medical and prescription coverage for at least 6 months before and at least 1 month following the NAFLD/NASH index date. The date of the first claim associated with the diagnosis of NAFLD/NASH was defined as the index date. The baseline or pre-index period was defined as the 6-month interval immediately preceding the index date. The follow-up period for eligible patients was defined as the time from the index date to one of the following, whichever was earliest: 1) progression to a different disease severity cohort, 2) 6 months after the index date, 3) end of coverage, 4) death, or 5) end of the study period.

The presence of ICD-9-CM or ICD-10-CM codes for progressive liver disease following the index date resulted in the categorization of patients into one of six non-mutually exclusive cohorts based on the severity of liver disease. The cohorts were incident NAFLD/NASH overall, NAFLD/NASH non-progressors, CC, DCC, LT, and HCC (**Figure 1**).

Endpoints

Patient age, sex, and region of residence as well as comorbid health conditions were characterized for the pre-index period for each of the disease severity cohorts. ICD-9-CM and ICD-10-CM codes were used to identify comorbidities, which included abdominal pain, anemia, bariatric surgery, cardiovascular disease (CVD), diabetes mellitus (type 1 and type 2), dyspepsia, hyperlipidemia, hypertension, insomnia, obesity, renal impairment, sleep apnea, thyroid disease, and vitamin D deficiency.

The primary endpoints were all-cause healthcare resource utilization and costs for the pre-index and post-index periods for each of the disease severity cohorts. Health care costs were expressed as per patient per month (PPPM) values and included outpatient, inpatient, and pharmacy

expenditures. Costs were adjusted to 2017 EUR. Measures of healthcare resource utilization included the number of readmissions per patient and average length of stay (LOS) per admission.

Statistical analysis

Descriptive statistics were calculated for all variables, including frequencies and percent responses for categorical variables and mean, median, and standard deviation (SD) for continuous variables. Resource utilization and costs were analyzed as continuous variables.

Chi-squared tests were used for the analysis of differences in categorical variables, and paired t-tests were used for comparisons of pre- and post-index healthcare resource utilizations and costs. *P*-values <0.05 were considered significant. Generalized linear models (GLM) with gamma error distribution and log-link function evaluated the incremental cost and resource utilization burden after adjustment for severity of liver disease and pre-index demographic and clinical characteristics. An important advantage of the GLM approach is that the log-transformed model is not subject to the assumptions that are necessary for a least-squares regression model, which are usually not held with cost data. For categorical variables, GLM estimates can be interpreted as percentage changes in cost. Explanatory variables included severity of liver disease, age, sex, geographic region, and comorbid conditions. All statistical analysis was performed with SAS version 9.4 [SAS institute, Cary, NC].

Results

The CMBD database included 36,856,032 patients for the period of January 1, 2006 through April 30, 2017, with 13,988 (0.04%) patients diagnosed with NAFLD/NASH (**Figure 2**). After applying the inclusion and exclusion criteria, 8,205 patients were eligible for inclusion in this analysis. Of these, 5,984 (72.9%) did not progress to a more advanced stage of liver disease and were

categorized as NAFLD/NASH non-progressors. A diagnosis of CC was confirmed in 139 (1.7%) patients, 2,028 (24.7%) were diagnosed with DCC, 115 (1.4%) had LT, and 61 (0.7%) progressed to HCC. Among patients diagnosed with cirrhosis (CC or DCC), 93.4% had a decompensated event at the time of their initial diagnosis of cirrhosis.

Demographic and clinical characteristics

The overall mean patient age was 58.4 years, ranging from 54.3 years for patients in the LT group to 70.9 years for those with HCC (**Table 1**). The majority of patients were male at 53.8% of all NAFLD/NASH patients, ranging from 52.2% of NAFLD/NASH non-progressors to 65.6% of those diagnosed with HCC.

Baseline rates of comorbid health conditions were high overall and in each of the disease severity cohorts. The most common comorbidities were hypertension, type 2 diabetes, and hyperlipidemia. The prevalence of comorbid health conditions was higher in patients with more advanced liver disease compared with those in the NAFLD/NASH non-progressors group. Similarly, the frequency of multiple comorbidities increased significantly as patients progressed to more severe liver disease (all $P<0.05$).

Healthcare resource utilization

The mean number of admissions was numerically greater during the pre- and post-index periods for patients with CC, DCC, LT, and HCC compared to those in the NAFLD/NASH no-progressors group. There were no significant changes in the mean number of hospital readmissions during the post-index period compared with those during the pre-index interval within each of the severity cohorts.

The shortest mean LOS per admission at baseline was 4.13 days for patients with NAFLD/NASH and no progression. Baseline LOS was significantly higher in each of the disease severity cohorts compared with NAFLD/NASH non-progressors at 8.11 days for CC patients, 10.74 days for DCC, days 6.12 for LT, and 9.08 days for HCC (**Figure 2**). There was a numerical increase in mean LOS from baseline to the post-index period at 5.74 days for NAFLD/NASH non-progressors, although this was not statistically significant. Mean LOS during the follow-up period was significantly higher from baseline within each of the disease severity cohorts, increasing to 9.98 days for those with CC, 13.86 days for DCC, 8.01 days for LT, and 11.99 days for patients with HCC.

Healthcare costs

Mean PPPM health care costs for the pre-index period were significantly lower for patients with NAFLD/NASH and no further progression compared to those with more severe liver disease (P<0.05 for all comparisons) (**Figure 3**). There was a significant increase in PPPM costs during the post-index period within each of the disease severity groups (all P<0.05). In addition, the increase in costs was significantly greater for patients with more severe liver disease compared to those with no evidence of progression (P<0.05 for all comparisons). Post-index total PPPM mean expenditures were also significantly higher for patients with DCC, LT, and HCC compared to those with CC (all P<0.05).

Within each disease severity cohort, higher costs from the pre-index to post-index periods were primarily associated with inpatient expenditures, which increased with the severity of liver disease. Inpatient PPPM costs during the post-index period accounted for 42% of the overall increase in health care expenditures for NAFLD/NASH non-progressors, 55% for those with CC, and 45% in the DCC, LT, and HCC cohorts. Significant predictors of higher, post-index health care

costs were patient age and selected comorbid health conditions including renal impairment, sleep apnea, anemia, CVD, and tobacco use (**Table 3**). After adjusting for severity of liver disease, as compared to NAFLD/NASH non-progressors (adjusted costs: €4,422), the cost of CC, DCC, LT and HCC was 1.13, 1.40, 2.37 and 1.55 times higher respectively, with adjusted costs being €5,014, €6,191, €10,501, and €6,869 respectively ($p<0.001$)(**Figure 4**).

Discussion

This real-world analysis of hospital data for patients with NAFLD/NASH confirms the substantial impact of NAFLD/NASH on healthcare systems in Spain. Hospital LOS for both the pre- and post-index periods was significantly longer for patients who progressed to more severe liver disease compared to those with NAFLD/NASH and no further progression. Expenditures during the pre-index period were significantly lower for the NAFLD/NASH non-progressors group compared to costs in patients with CC, DCC, LT, and HCC. Similarly, post-index PPPM costs within each of the disease severity groups were significantly higher than those for patients who experienced no disease progression. The primary driver of cost increases from baseline to the post-index period were inpatient services, which accounted for 45% to 55% of the increase in expenditures for CC, DCC, LT, and HCC patients. Total costs for patients with more severe liver disease remained higher compared with patients without progression after adjusting for demographic and clinical characteristics.

The study findings are consistent with previous researches that report a substantial impact of NAFLD/NASH on healthcare resource utilization and costs, particularly for patients with more severe liver disease.[1,3,5,25-27,37,41] A recent analysis of commercially insured patients in the US

reported a 41% increase in the number of inpatient hospital admissions and a 61% increase in the mean number of admissions following a diagnosis of CC. Per patient per year mean total health care costs rose from $25,738 (pre-diagnosis) to $36,558 (post-post-diagnosis).[41] Similarly, a retrospective cohort analysis of NAFLD/NASH patients enrolled in Medicare studies reported higher inpatient and outpatient charges for CC and DCC patients compared with noncirrhotic NAFLD patients. Compared with CC patients, those with DCC had higher total inpatient and outpatient charges.[26]

However, many of these analyses are specific to the US[26,37,42] and most estimates of the economic impact of NAFLD/NASH in Europe and other countries have been generated by predictive models.[1,3,5,13,27] While informative, there are important limitations in the methodologies used to generate these estimates, including variability in the methods used to ascertain a clinical diagnosis of NAFLD and NASH; use of older data that may not accurately represent current patterns and trends in factors such as rates of obesity and diabetes; lack of consistency in techniques, terminology, and classification systems for fibrosis and cirrhosis stage; inclusion of data from studies that relied on small sample sizes or had short follow-up durations; and between-study variations in study aims and population characteristics.[1,7] This real-world analysis provides a current and more accurate perspective on patterns of healthcare resource utilization and direct medical costs that are associated with NAFLD/NASH in Spain. Such information can be used to guide the development of interventions to improve the management of patients with NAFLD/NASH in the Spanish healthcare system as well as monitor the impact of such interventions.

This analysis also attempted to highlight the prevalence and impact of comorbidities in NALFD/NASH by severity of liver disease. Across the liver disease cohorts, we found that 15% to 45% of patients had at least one comorbid condition and the frequency of comorbid health conditions increased as patients progressed from incident NAFLD/NASH to more severe liver disease. Previous studies also report an association of NAFLD/NASH and various comorbidities such as CVD,[8,26] obesity, insulin resistance, type 2 diabetes, hypertension, and hyperlipidemia, with each of these disorders characteristic of the metabolic syndrome.[6,8-11,14,16,17,43,44] In this Spanish population, we found that renal impairment, anemia, sleep apnea, and smoking were also associated with increased severity of liver disease and may have contributed to the higher costs and service utilization observed in these patients. Ongoing monitoring and management of all comorbid health conditions, including those that might be more typical of patients receiving care in Spain, may allow public health approaches to be targeted to the specific risk profile of patients in the Spanish healthcare system and may optimize the use of health care resources and budgets.

As the prevalence of NAFLD/NASH and associated comorbidities continues to increase worldwide, the need for public health interventions and initiatives that are tailored to the unique demographic and clinical characteristics of patients residing in diverse regions of the world will be of critical importance.[6,7,45] Such an approach will rely on improvements in the identification of patients with progressive disease in the absence of symptoms, initiation of pharmacological and lifestyle interventions to address the metabolic and cardiovascular comorbidities that are characteristic of NAFLD/NASH, and promotion of the recommended lifestyle interventions to prevent or slow disease progression. Optimal clinical management combined with efforts to

reduce and manage risk factors for mortality and disease progression have the potential to decrease healthcare resource utilization and costs, especially when considered over the duration of disease. Such efforts are particularly important in the absence of noninvasive screening and diagnostic tests for NAFLD and approved pharmacotherapies for the treatment of NAFLD/NASH.

Consideration of regional and between-country variations in demographics, geography, and historical factors will be essential when planning a comprehensive program for Spain to address the current and future impact of NAFLD/NASH. An accurate understanding of the epidemiologic burden of NAFLD/NASH, including changes over time and factors that may be associated with poor clinical outcomes or greater need for healthcare resources will form the basis of a strong NAFLD/NASH public health initiative in Spain with the potential to reduce the future burden of NAFLD/NASH.[39]

The retrospective study design and use of a hospital discharge records database, which relies on administrative claims data for disease identification and assessment, are two important limitations of this analysis. Data for the CMBD are primarily collected for accounting purposes, and the information is subject to data coding limitations, data entry errors, and misclassification of NAFLD/NASH and liver disease severity. In addition, the CMBD may not be fully representative of the entire population of Spain, and the patterns of healthcare resource utilization and costs in this study may not apply to the general population of Spanish patients with NAFLD/NASH who are not included in the CMBD.

The identification of patients with advanced liver disease was limited to ICD-CM-09 and ICD-CM-10 codes rather than laboratory or biopsy data or other measures of fibrosis such as elastography

and ultrasound. This may have resulted in an underestimation of the true number of patients who experienced disease progression in the case of asymptomatic disease progression. Patients could have had more severe disease before their initial NASH/NAFLD diagnosis, and the incident NAFLD/NASH non-progressor group might have included F0-F3 patients as well as undiagnosed F4 (CC) patients due to under-coding and lack of ICD codes for F0-F3. Moreover, since CMBD includes hospitalized patients in Spain, the estimates reported here for severe liver diseases could have be inflated due to patients being comparatively sicker. Finally, several potentially important factors were controlled for in these multivariable analyses, but adjustment was limited to characteristics that could be measured with data that were available.

While these are important limitations, this study has several strengths. The analysis was based on a large cohort of NAFLD/NASH patients at varying stages of disease severity. The study tracked patients' progression or non-progression through CC, DCC, LT, and HCC. The inclusion criteria required patients to have at least one-month follow-up after the post-index date. This criterion preserved sample size and may have reduced bias associated with a longer follow-up interval in healthier patients who did not die or progress to a more advanced stage of liver disease.

In conclusion, patients with more severe liver disease were more likely to experience one or more comorbid health conditions, use more health care resources and incur higher costs compared to those with no evidence of disease progression. The primary cost drivers were associated with inpatient services. These findings highlight opportunities to improve overall patient management and ensure optimal allocation of healthcare resources and control costs associated with NAFLD/NASH in Spain.

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Figures

Figure 1. Patient disposition

Group	Patients, n
All patients in the Spanish hospitalization database with at least one day of enrollment from 01/01/2006 to 04/30/2017	36,856,032
All patients with ≥1 ICD-10-GM code for NAFLD/NASH from 01/01/2006 to 04/30/2017 [date of first diagnosis is the index date]	13,988
All patients with ≥1 ICD-10-GM code for NAFLD/NASH from 01/01/2006 to 04/30/2017 and no diagnosis of NAFLD/NASH from 01/01/2005 to 01/01/2006: incident NAFLD/NASH	12,022
Continuous enrollment with medical and pharmacy benefits for ≥6 months before the index date: pre-index period	11,908
Continuous enrollment with medical and pharmacy benefits for ≥1 month after the index date: post-index period	11,785
Adult patients (≥18 years of age) at the time of the index date	11,434
No evidence of exclusionary diagnoses	8,205

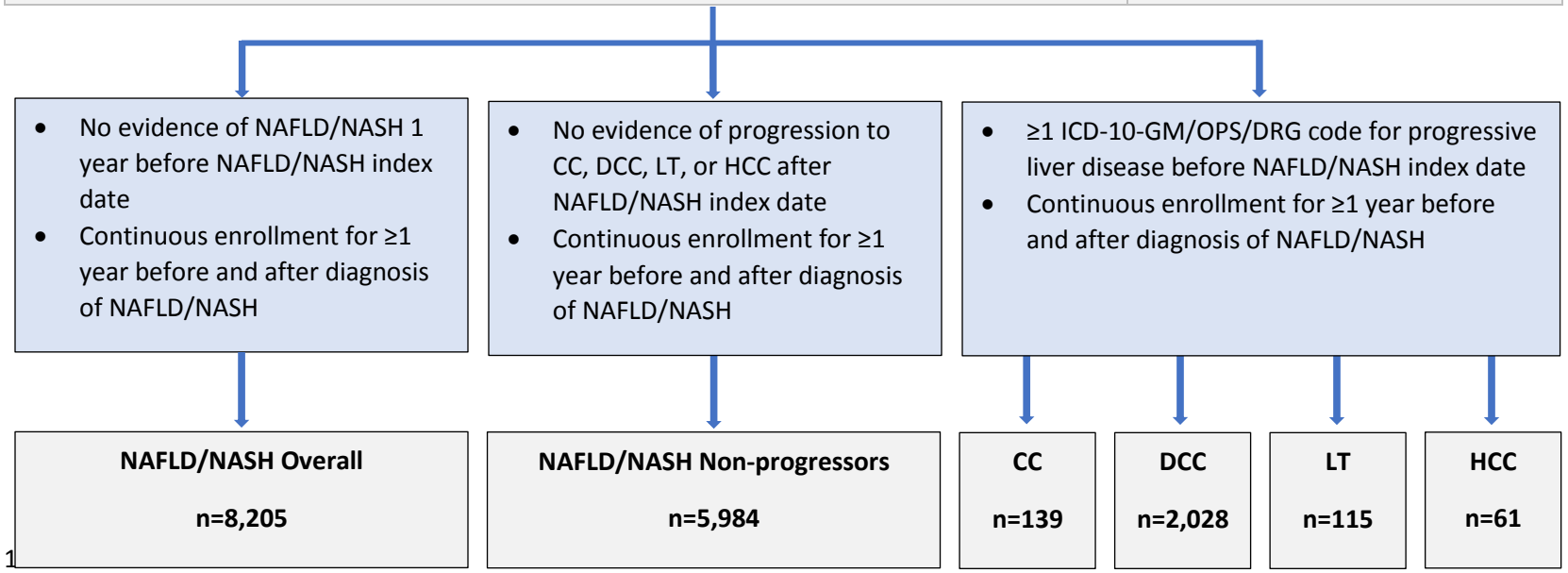
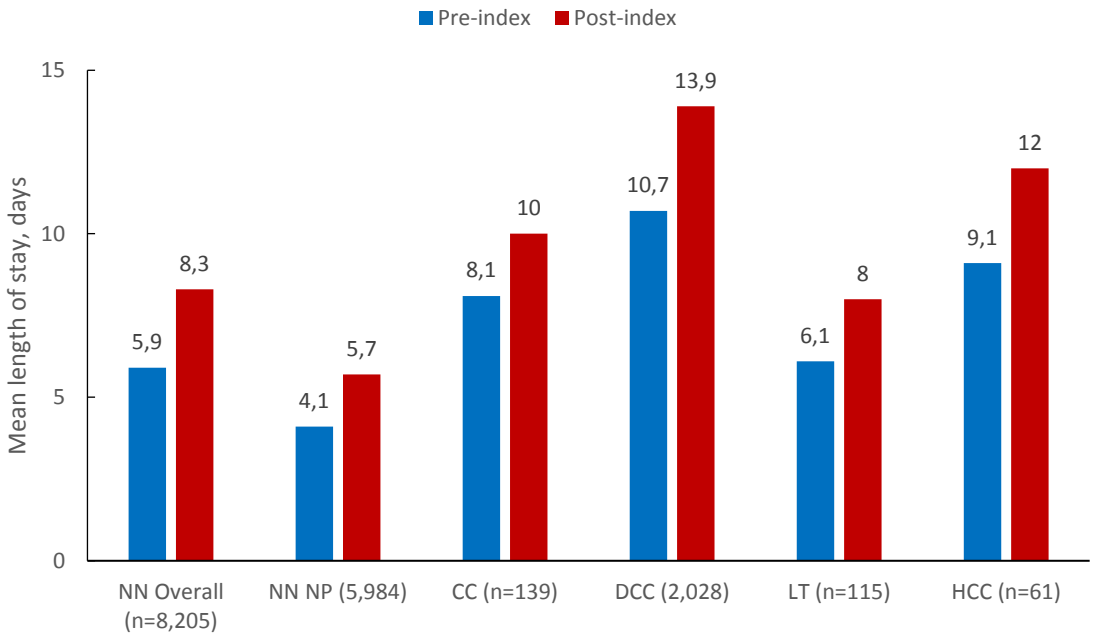


Figure 2. Pre- and post-index average length of stay per admission by severity of liver disease



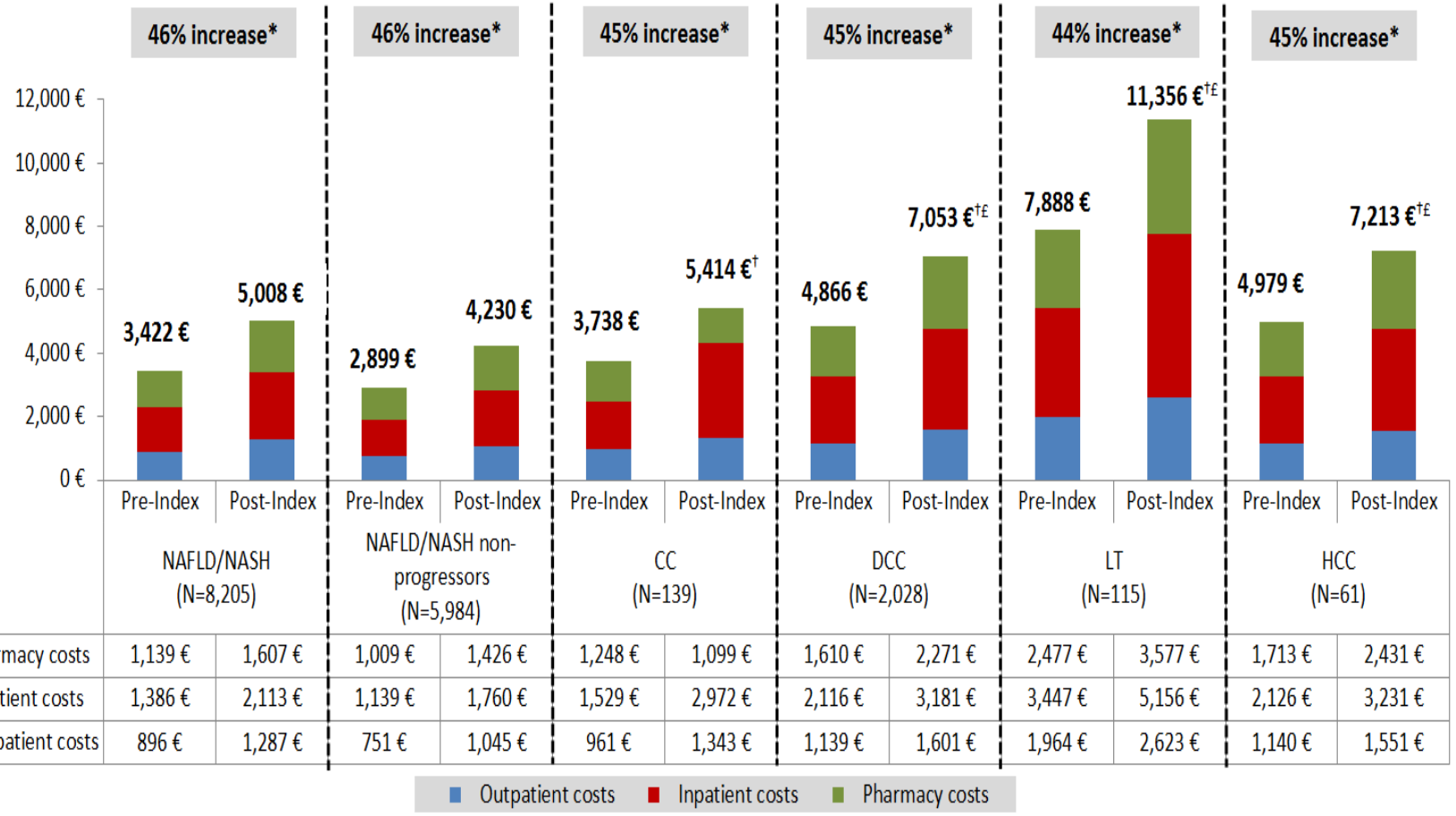
All comparisons with NAFLD/NASH non-progressors or CC were statistically significant (*P*<0.05).

GLM model adjusted for age, sex, region, and comorbid health conditions (abdominal pain, anemia, apnea, bariatric surgery, cardiovascular disease, type 2 diabetes, dyspepsia, hyperlipidemia, hypertension, insomnia, obesity, renal impairment, smoking, thyroid disease, vitamin D deficiency).

CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma;

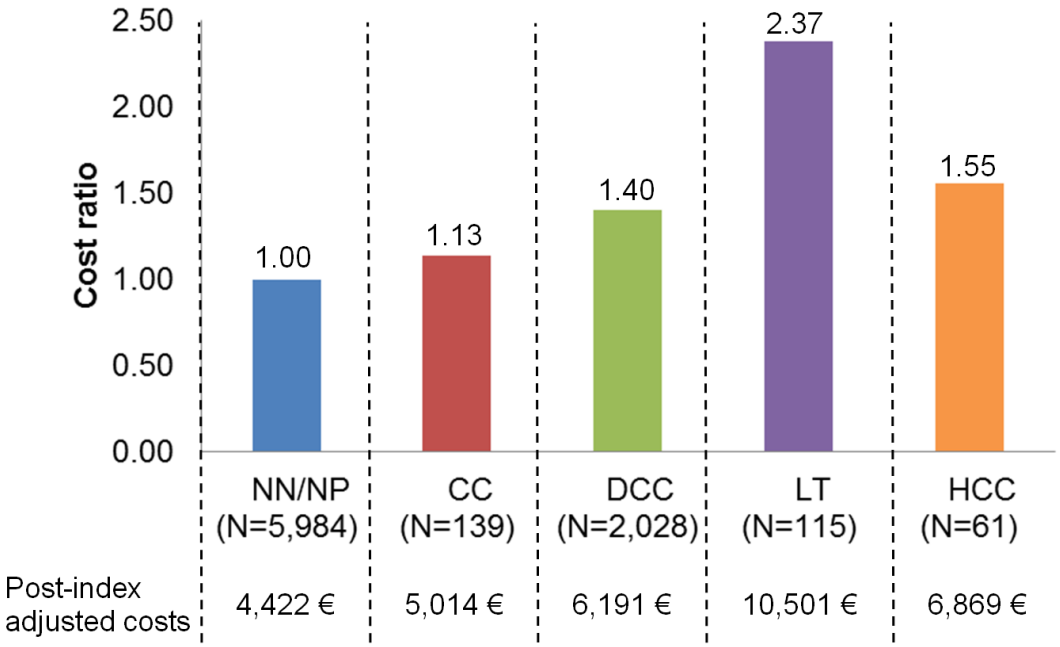
LT, liver transplantation; NN, NAFLD/NASH; NN NP, NAFLD/NASH non-progressors.

Figure 3. Pre- and post-index all-cause per patient per month health care costs by severity of liver disease



*P<0.05 for pre-index vs post-index comparisons; †P<0.05 for post-index NAFLD/NASH non-progressors vs post-index CC/DCC/LT/HCC comparisons; £P<0.05 for post-index CC vs post-index DCC/LT/HCC

Figure 4. Multivariable adjusted per patient per month all-cause health care costs by severity of liver disease: Post-index period



CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplantation; NN NP, NAFLD/NASH non-progressors.

Tables

Table 1. Baseline demographic and clinical characteristics

	Severity of Liver Disease					
	NAFLD/NASH Overall (N=8,205)	**NAFLD/NASH Non-progressors (n=5,984)**	**CC (n=139)**	**DCC (n=2,028)**	**LT (n=115)**	**HCC (n=61)**
Demographics						
Age, years						
Mean (SD)	58.4 (16.6)	54.8 (15.9)	65.2 (14.2)	68.8 (14.4)	54.3 (11.8)	70.9 (11.4)
Age group, years, n (%)						
18-44	1,824 (22.2)	1,671 (27.9)	9 (6.5)	131 (6.5)	18 (11.6)	0 (0.0)
45-64	3,305 (40.3)	4,313 (72.1)	56 (40.3)	565 (27.9)	76 (49.0)	16 (26.2)
≥65	3,076 (37.5)	1,677 (28.0)	74 (53.2)	1,332 (65.7)	21 (13.6)	45 (73.8)
Sex, n (%)						
Female	3,793 (46.2)	2,859 (47.8)	57 (41.0)	878 (43.3)	24 (20.9)	21 (34.4)
Male	4,412 (53.8)	3,125 (52.2)	82 (59.0)	1,150 (56.7)	91 (79.1)	40 (65.6)
Region, n (%)						
Andalusia	964 (11.7)	677 (11.3)	36 (25.9)	260 (12.8)	10 (6.5)	15 (24.6)
Catalonia	1,395 (17.0)	959 (16.0)	16 (11.5)	366 (18.1)	75 (48.4)	13 (21.3)
Galicia	687 (8.4)	561 (9.4)	5 (3.6)	123 (6.1)	0 (0.0)	2 (3.3)

Madrid Valencian Community	1,464 (17.8) 997 (12.2)	994 (16.6) 779 (13.0)	13 (9.4) 22 (15.8)	447 (22.0) 193 (9.5)	19 (12.3) 0 (0.0)	18 (29.5) 0 (0.0)
Comorbid Health Conditions						
Abdominal pain	178 (2.2)	158 (2.6)	0 (0.0)*	19 (0.9)*†	1 (0.9)*	0 (0.0)*
Anemia	984 (12.0)	367 (6.1)	33 (23.7)*†	597 (29.4)*†	7 (6.1)*†	16 (26.2)*†
Apnea	123 (1.5)	92 (1.5)	1 (0.7)*	31 (1.5)*	0 (0.0)*	1 (1.6)*
Bariatric surgery	1 (0.0)	1 (0.02)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiovascular disease	726 (8.8)	365 (6.1)	13 (9.4)*	353 (17.4)*†	1 (0.9)*†	5 (8.2)*†
Diabetes mellitus, type 1	39 (0.5)	32 (0.5)	1 (0.7)*	7 (0.4)*	0 (0.0)*	0 (0.0)*
Diabetes mellitus, type 2	1,656 (20.2)	965 (16.1)	37 (26.6)*	657 (32.4)*†	17 (14.8)*†	19 (31.1)*†
Dyspepsia	208 (2.5)	130 (2.2)	5 (3.6)*	74 (3.7)*†	1 (0.9)*	1 (1.6)*
Hyperlipidemia	1,204 (14.7)	932 (15.6)	16 (11.5)*	258 (12.7)*†	2 (1.7)*†	6 (9.8)*†
Hypertension	2,299 (28.0)	1,476 (24.7)	45 (32.4)*	776 (38.3)*†	19 (16.5)*†	24 (39.3)*†
Insomnia	8 (0.1)	4 (0.07)	0 (0.0)	4 (0.2)	0 (0.0)	0 (0.0)
Obesity	569 (6.9)	424 (7.1)	12 (8.6)*	136 (6.7)*†	5 (4.4)*†	0 (0.0)*†
Renal impairment	643 (7.8)	252 (4.2)	16 (11.5)*	376 (18.5)†	11 (9.6)*	10 (16.4)*
Smoking	963 (11.7)	677 (11.3)	18 (12.9)*	267 (13.2)*†	7 (6.1)*†	6 (9.8)*†

Thyroid disease	491 (6.0)	331 (5.5)	12 (8.6)*	151 (7.5)*†	3 (2.6)*†	3 (4.9)*†
Vitamin D deficiency	32 (0.4)	26 (0.4)	0 (0.0)*	6 (0.3)*	0 (0.0)*	0 (0.0)*
Multiple Comorbid Health Conditions						
CVD AND diabetes (type 1 or 2) AND renal disease	236 (2.9)	50 (0.8)	4 (2.9)*	62 (3.1)*†	0 (0.0)*	3 (4.9)*
CVD OR diabetes (type 1 or 2) OR renal disease	1,727 (21.0)	1,034 (17.3)	35 (25.2)*	690 (34.1)*†	16 (13.9)*†	16 (26.2)*†
At least 1 of 5 comorbidities¶	3,648 (44.5)	1,190 (19.9)	33 (23.7)*	738 (36.4)*†	17 (14.8)*†	18 (29.5)*†
At least 2 of 5 comorbidities¶	1,959 (23.9)	454 (7.6)	14 (10.1)*	319 (15.7)*†	3 (2.6)*†	9 (14.8)*
At least 3 of 5 comorbidities¶	782 (9.5)	108 (1.8)	4 (2.9)*	101 (5.0)*†	0 (0.0)*	3 (4.9)*

Baseline period defined as 6 months preceding the index date. ¶CVD, diabetes, hyperlipidemia, hypertension, renal disease. *P<0.05 for comparison with NAFLD/NASH non-progressors. †P<0.05 for comparison with CC.

CC, compensated cirrhosis; CVD, cardiovascular disease; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplantation; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; SD, standard deviation.

Table 2. Multivariate adjusted model for per patient per month total cost

Parameter at Baseline*	**Cost Ratio**	**95% CI**	***P*-value**
Age			
18-44	Reference	---	---
45-64	1.08	1.04, 1.12	0.000
≥65	1.16	1.11, 1.21	0.000
Sex			
Male	Reference	---	---
Female	1.01	0.98, 1.04	0.427
Region†			
Andalusia	0.98	0.94, 1.03	0.535
Catalonia	0.92	0.88, 0.96	0.000
Galicia	0.96	0.90, 1.01	0.107
Madrid	0.97	0.93, 1.02	0.152
Valencian Community	0.89	0.85, 0.93	0.000
Liver disease severity			
NAFLD/NASH non-progressors	Reference	---	---
CC	1.13	0.98, 1.32	0.099
DCC	1.40	1.35, 1.45	0.000
LT	2.37	2.10, 2.69	0.000
HCC	1.55	1.32, 1.83	0.000
Comorbid health condition#			
Abdominal pain	0.93	0.84, 1.03	0.145
Anemia	1.10	1.05, 1.15	0.000
Apnea	1.12	0.99, 1.26	0.062
Bariatric surgery	2.87	0.80, 10.36	0.107
CVD	1.07	1.01, 1.13	0.013
Diabetes mellitus, type 1	1.12	0.91, 1.38	0.294
Diabetes mellitus, type 2	1.00	0.96, 1.04	0.971
Diabetes mellitus, other	0.97	0.83, 1.13	0.669
Dyspepsia	1.03	0.94, 1.13	0.492
Hyperlipidemia	1.00	0.96, 1.05	0.850
Hypertension	1.03	0.99, 1.07	0.149
Insomnia	0.98	0.83, 1.13	0.940
Obesity	1.05	0.99, 1.72	0.131
Renal impairment	1.63	1.54, 1.72	0.000

Tobacco use	1.05	1.00, 1.10	0.033
Thyroid disease	1.00	0.94, 1.06	0.978
Vitamin D deficiency	1.29	1.03, 1.62	0.028

*Baseline period defined as 6 months preceding the index date. †Reference: patients from other regions. #Reference: patients without comorbidity.

CC, compensated cirrhosis; CI, confidence interval; CVD, cardiovascular disease; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplantation; NN, NAFLD/NASH; NN NP, NAFLD/NASH non-progressors.

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