Direct medical costs of Non-alcoholic Fatty Liver Disease (NAFLD) in Catalonia at the hospital level: a retrospective multicenter study

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Abstract

Background: The prevalence of non-alcoholic fatty liver disease (NAFLD) is increasing worldwide, which is expecting to correlate with significant medical and social costs. This study aimed to evaluate the clinical and economic burden of NAFLD in Catalonia at the hospital level.

Methods: Records of all patients diagnosed with NAFLD and treated in Catalan hospitals between the year 2007 and 2018 were extracted from a patient-level healthcare database.

Results: Admission files of 24,172 individual patients were obtained. High comorbidity rates were found across age groups, with a mean Charlson Comorbidity Index of 5.1. In-hospital mortality rate increased over the study period, and was associated to a higher comorbidity rate. Disease complexity was increased in this patient group, which is associated with larger medical costs. The mean annual cost per patient was €4073, with a total annual direct medical cost of €27,370,827. The greatest portion of costs was attributed to surgical interventions (€14,429,336).

Conclusions: The high level of comorbidity and disease complexity in this patient group versus the general population is expected to correlate with a more intensive use of medical resources and costs. This study provides novel data to inform resource allocation and disease management decisions at the regional level.

Keywords: Nonalcoholic Fatty Liver Disease; Nonalcoholic Steatohepatitis; Multimorbidity; Medical Care Costs.

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1. Background

Non-alcoholic fatty liver disease (NAFLD) comprises several conditions, from non-inflammatory isolated steatosis to non-alcoholic steatohepatitits (NASH), in which substantial liver damage is present [1]. NAFLD is considered to be a hepatic manifestation of metabolic syndrome and is strongly associated with obesity and visceral adiposity, insulin resistance, type 2 diabetes mellitus, and dyslipidemia [2-4].

NAFLD/NASH cause major liver damage, and can progress to fibrosis, leading to cirrhosis and hepatocellular carcinoma, the sixth most common cancer type in the world [5]; in Spain, 6595 new liver cancer cases were estimated for the year 2020 and it was the sixth most common cancer-related cause of death with a 5-year survival rate of 16.4% in males and 15.5% in females (2018 data) [5].

NAFLD is an expanding health concern worldwide, affecting approximately the 25% of the population worldwide, and about the 23% in Europe [6, 7]. The increasing prevalence of NAFLD is expected to correlate with significant medical and social costs; however, detailed economic evaluations are, at present, still scarce. A recent study analyzing the burden of NAFLD/NASH in France estimated a mean annual cost of €7736 per patient at the hospital level, increasing with the worsening of patients' condition [8]. Similarly, in Italy, the mean annual cost of inpatient services was €8762 per patient [9]. Previous studies estimated patient costs of between €354 and €1163 per patient in various European countries (Germany, France, Italy and the United Kingdom) [10]. Great variability is displayed in available studies, and despite the efforts done to quantify the costs that derive from NAFLD/NASH, main cost drivers have not been analyzed.

Moreover, the patient population diagnosed with NAFLD and NASH in Catalonia and in Spain is not well characterized. Real-world data on hospital resource utilization and costs allows an increased understanding of patients' characteristics and the specific needs of patients and physicians, and enables the application of measures reflecting current clinical practice and disease complexity [11].

In Catalonia, the data analytics program for health research and innovation (Programa d'analítica de dades per a la recerca i la innovació en salut, PADRIS) has been developed to collect detailed patient-level data of healthcare usage and patient characteristics [12]. This linkage program aimed to connect various administrative records from a single patient, to associate social and medical information. PADRIS represents a useful tool for the examination of disease management in order to develop new protocols that reflect the disease complexity within the population.

In this context, this study aimed to describe the characteristics of patients with NAFLD in Catalonia, and to evaluate use of hospital resources and the associated medical costs over a 10-year period.

2. Methods

2.1. Study setting

Records of all patients diagnosed with NAFLD in the region of Catalonia (7.5 million inhabitants) between 2007 and 2018 were extracted from the PADRIS database via ethics committee approval. All hospital admissions were analyzed in a multicenter retrospective study. Within the database, diagnoses and medical procedures were coded by means of the International Statistical Classification of Diseases and Related

Health Problems, 9th version (ICD-9) and 10th version (ICD-10) [13, 14]. The Health Evaluation and Quality Agency of Catalonia assures data consistency and reliability.

2.2. Data extraction

NAFLD patients were ascertained using the ICD-9 codes: 571.8, 571.9; and ICD-10 codes: K76.0, K75.81**.** Patients diagnosed with viral hepatitis, autoimmune liver disease, HIV, alcoholism or alcoholic liver disease during the study period were excluded from the study.

All parameters identifying healthcare centers or medical history were re-coded within healthcare centers to maintain records anonymized, in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. This research did not involve human participants and there was no access to identifying information.

2.3. Study variables

The coded variables included in the analysis were: patients' sex and age group, type of admission (scheduled or urgent), type of discharge (including death), admission motive, up to 15 secondary diagnoses registered during the admission and to the first 26 medical procedures the patient is subjected to during the admission.

Subsequently, patient classification into adjusted morbidity groups (GMA) was obtained. This risk stratification tool classifies patients into distinct GMA groups automatically according to the number of chronic diseases and into 5 levels of complexity, via the assessment of patients' relative risk [15]. This tool allows to refine disease evaluations and to predict outcomes in the use of healthcare resources (number of hospitalizations, ambulatory visits and pharmaceutical expenses), and is comparable to other existing morbidity groupers as the Adjusted Clinical Groups (ACG) and the Clinical Risk Group (CRG) [16]. GMA is constructed combining morbidity group

and complexity level. Morbidity groups are constructed using the diagnosis codes registered for each patient, classifying the patients in those with acute, chronic and oncologic diseases, and according to the number of systems affected with chronic diseases [15]. Complexity was calculated using quali-quantitative models with the information on morbidity and mortality, hospitalization rate and pharmaceutical expenses in the total population of Catalonia in 2011 [15]. Complexity stratifies the population in 5 levels, obtained identifying 4 cut-off points from the 40^{th}, 70^{th}, 85^{th} and 95^{th} percentiles of complexity in each morbidity group [15]. This correlation provided qualitative complementary data on NAFLD medical costs.

2.4. Data analysis

Individual patient data was used for the analysis of patients' characteristics. The first admission due to NAFLD registered per patient in the study period was used for this analysis. All admission files were used to analyze data on the nature of admission and admission costs. Data was analyzed considering 3 age groups: < 60 years of age, ≥ 60 and < 80 years, and ≥ 80 years of age.

In-hospital mortality was calculated as the annual number of deaths registered within all patients registered with NAFLD in the database. The Charlson Comorbidity Index (CCI) was calculated to assess patient comorbidity status [17, 18]. CCI of deceased patients was measured using the data from the admission in which death was registered.

Direct medical costs associated with the use of healthcare resources were calculated based on the mean cost of admissions and medical procedures determined by the Catalan government updated for the year 2020 [19, 20]. These figures include all expenses related to the admission: treatment (examination, medication and

palliative/surgical care), nutrition, costs associated to personnel, medical equipment and resources. Admission cost was calculated by multiplying the unit cost of medical procedures by the number of procedures registered during the admission.

Statistical analyses are applied to individual patient files or all admission files for the analysis of patient characteristics or use of resources, respectively. Normality was tested with the Kolmogorov-Smirnov test. Frequencies and percentages are presented for dichotomous variables and mean and standard deviation (SD) or median and interquartile range (IQR) were calculated for quantitative variables. The Spearman's rank correlation coefficient was calculated to assess temporal trends in in-hospital mortality and costs. Two-tailed non-parametric independent t-test (Mann-Whitney U test) or one-way analysis of variance (Kruskal-Wallis test) were used as appropriate and two-sample Z tests were used to test for differences in sample proportions, with a $p<0.05$ considered statistically significant. Statistical analyses were performed using Microsoft Excel© Professional Plus 2010 (Microsoft Corporation, Redmond, WA, USA) and StataSE 12 for Windows (StataCorp LP. 2011. Stata Statistical Software: Release 12. College Station, TX, USA).

3. Results

3.1. Patient demographics and clinical characteristics

In total, 150,236 hospital admission files were claimed, corresponding to 24,172 individual patients. On average, 6.2 admissions were registered per patient, 76.6% of patients were admitted into hospital settings between 1 and 8 times over the study period, 18.9% of patients were admitted between 9 and 16 times, and 4.5% of patients were admitted over 17 times. Of all patients, 60.0% (95%CI, 59.4 to 60.6) were males,

and 79.3% were over 60 years of age (Table 1). High comorbidity rates were found across patient groups; mean CCI was 5.1 in the total patient population. Furthermore, CCI increased significantly with patients' age (< 60 years vs. ≥ 60 < 80 years, p<0.0001; ≥ 60 < 80 years vs. ≥ 80 years; p<0.0001), yet, mean CCI did not vary over the study period. The most frequent comorbid conditions registered upon admission were liver cirrhosis, essential hypertension, type II diabetes mellitus, ascites and portal hypertension, all found in more than 15% of admissions. Over the study period, a hepatocellular carcinoma was registered in 12.9% of admissions in patients hospitalized with NAFLD (5962 patients). Great variability was found in the admitting diagnoses, corresponding the most frequent with the conditions in table 1: 7.2% of admissions were due to non-alcoholic liver cirrhosis, 6.9% due to hepatocellular carcinoma, and a large number of conditions were found in frequencies under 5%.

Most of the admissions (49.5%) corresponded to patients between 60 and 80 years of age, and the percentage of admissions in this age group increased significantly over the study period (p<0.0001), reaching the 56.0% in 2018 (Figure 1A). The admissions of patients under 60 years of age slowly increased over the study period, whereas, those of patients over 80 years of age decreased. Interestingly, in-hospital mortality rate increased over the study period for all age groups (p<0.0001) (Figure 1B); and increased significantly with patients' age (< 60 years vs. ≥ 60 < 80 years, p<0.0001; ≥ 60 < 80 years vs. ≥ 80 years; p<0.0001) (Table 1). No significant differences appeared in the in-hospital mortality rate between males and females; contrarily, in-hospital mortality rate increased significantly with CCI (CCI ≤4 =15.6%; CCI >4 ≤8 =34.1%; CCI >8 =82.7%).

In-hospital mortality was associated with a higher incidence of liver cirrhosis (56.1% vs. 35.2% in non-deceased patients), ascites (33.3% vs. 17.3% in non-deceased patients), hepatocellular carcinoma (20.1% vs. 12.5% in non-deceased patients), hepatic encephalopathy (29.1% vs. 9.7% in non-deceased patients), atrial fibrillation (11.3% vs. 8.6% in non-deceased patients), acute kidney failure (32.4% vs. 7.1% in non-deceased patients), and chronic kidney disease (9.5% vs. 5.9% in non-deceased patients), among other conditions (Table 2). In addition, CCI was significantly higher in patients deceased during the hospitalization (deceased vs. non-deceased; $p<0.0001$).

The analysis of GMA codes confirmed the high comorbidity rate in this patient population; 80.2% of patients were diagnosed with chronic conditions in 4 or more systems and 15.2% presented an active carcinoma (Table 3). Most of the patients (78.2%) were assigned to the complexity level 3 or above, a percentage considerably higher to the estimated in the general population (20.0%) (Figure 2).

3.2. Use of medical resources and costs

Almost 60% of all admissions corresponded to urgent admissions, although medical procedures registered upon admission were principally diagnostic procedures (Table 4). Overall, 1303 liver transplants were registered over the study period, while 6858 patients had a previous history of liver transplant; only 6 liver transplants were registered in patients over 80 years of age (0.013% of admissions in patients in that age group).

Medical costs were calculated at the hospital level based on medical procedures and required care. Mean annual cost per patient was €4073, €7641 in patients under 60 years of age, €4552 in patients between 60 and 80 years of age, and €3165 in those

over 80 years of age; significant changes over time were only registered in patients under 60 years of age ($p<0.0001$) (Figure 3A).

The total annual medical cost of NAFLD was €27,370,827, at the hospital level (Table 5); the largest costs corresponded to the group of patients between 60 and 80 years of age. Despite being the most frequent, diagnostic imaging procedures did not represent the largest portion of costs; €14,429,336 of the total cost was attributed to surgical interventions. Finally, total annual costs increased over the study period in patients under 60 years of age ($p<0.0001$) and decreased in those over 80 years of age ($p=0.0027$) (Figure 3B).

4. Discussion

The prevalence of NAFLD is increasing worldwide and is expected to continue to grow in parallel with the increasing prevalence of obesity and diabetes mellitus, which is expected to cause an increase of the medical and social costs associated [6, 21]. The calculation of the burden associated to NAFLD/NASH has been limited by disease complexity and the availability of incidence and healthcare usage data. In addition, the elevated comorbidity rate in this patient population hampers the estimation of the burden of NAFLD/NASH separately from their comorbidities. This study aimed to evaluate the characteristics of patients with NAFLD/NASH in Catalonia and their use of hospital resources and associated medical costs.

One attempt to estimate the clinical burden of NAFLD in the United States and four European countries (Germany, France, Italy and the United Kingdom) measured direct costs that could reach the €89 ($103) billion, €1387 ($1613) per patient, in the United States, and between €4 and €12 billion in total, between €354 and €1163 per patient,

in the aforementioned European countries in 2016 [10]. In 2019, The Global Assessment of the Impact of NASH (GAIN) study estimated a NASH-related direct medical costs in Spain of €2162 per patient via online survey [22]. More recently, estimations in France and Italy pointed to higher annual medical costs per patient, reaching the €7736 and €8762 per patient at the hospital level [8, 9]; €9748 ($11,346) per patient in the United States in patients with no disease progression, taking into account outpatient and inpatient care [23]. The large variability observed in cost estimations may be a consequence of the distinct methods that are used, the inclusion or exclusion of primary care costs and pharmaceutical costs or societal costs, and the different patient populations that are evaluated.

In Catalonia, the direct medical cost of hospital care estimated in the present study was €4073 per patient, with a total annual cost of €27,370,827 at the hospital level. The highest costs per patient were measured in patients under 60 years of age (€7641), however, the largest portion of costs corresponded to patients between 60 and 80 years of age, the most numerous patient group. A similar study based on the same database estimated a total medical cost of cirrhosis in Catalonia in 2013 of €4234 per patient [24]. In all cases, comparisons with evaluations in other evaluations or countries should consider the aforementioned variables.

The patient population observed in this study was comparable to that in other European countries [8, 9]. High comorbidity rates were observed in this population, measured via CCI and GMA, associated to conditions that included essential hypertension, type II diabetes, anemia and kidney failure among others, all extensively described in patients with NAFLD/NASH [25-27]; in addition, multiple conditions affecting the liver were registered, comprising non-alcoholic cirrhosis, ascites, portal

hypertension, hepatocellular carcinoma or hepatic encephalopathy. Previous population studies in Germany identified NAFLD as a risk factor for the development of coronary heart disease, myocardial infarction, atrial fibrillation and chronic kidney disease [28, 29]. Similarly, NAFLD was found to constitute a risk factor for the development of depression and anxiety, however, these pathologies were not identified in this study [30]. Overall, the system indicated a high proportion of patients with multiple chronic conditions affecting more than 4 systems (80.2%), this proportion was 23.5% in the total Catalan population in 2016 [31]. Moreover, 57% of patients were considered to have a disease complexity level of 4 or 5, while this group represents the 5% of the general population. This increased complexity is expected to correlate with a more intensive use of healthcare resources [15]. Despite the inherent high comorbidity level found in patients with NAFLD/NASH, the increased rate of diagnosis of comorbid conditions calculated herein could be influenced by the exclusion of primary care data: only hospital admissions are analyzed, often required by patients in a worse condition when compared to primary care.

In-hospital mortality was 31.2% over the study period, increasing with patients' age. Interestingly, mortality rate increased over the study period for all age groups. In-hospital mortality was higher in patients over 80 years of age, which could be one of the factors behind the decrease of admissions registered in this group. In general terms, mortality was associated with a worsening of patients' condition and higher comorbidity rates; however, it must be considered that CCI in deceased patients was measured at the moment of death and that the remaining population was calculated in the first registered admission, limiting comparability. Further studies will be

required to evaluate the evolution of the NAFLD/NASH-associated in-hospital mortality and its correlation with patients' comorbidity status.

Hospital admissions of NAFLD patients evaluated in this study showed the central role of diagnostic imaging procedures, followed by surgical interventions (biopsies, tissue lesion removal or transplants, among others). Surgical procedures represented the greatest portion of medical costs annually (€14,429,336). Other interventions including diet or exercise recommendations, relevant in the initial management of NAFLD, were not registered in this database [32]. This study was subjected to a series of limitations. Firstly, despite the efforts focused on increasing the percentage of coding carried out by specialized coding units, possible errors and variability may arise from the codification process. Similarly, the lack of an exact concordance between ICD-9 and ICD-10 NAFLD/NASH codes may generate variability between 2015 and 2016, when the system was updated; in fact, several evaluations measured significant differences in mortality calculations when using data coded via ICD-9 and ICD-10 codes [33, 34]. The inclusion of all codes corresponding to NAFLD/NASH in both systems aimed to reduce this bias. Secondly, imaging and biopsy results were not available to accurately evaluate disease progression. Thirdly, data codification did not allow the calculation of costs prior and after the diagnosis of NAFLD/NASH. In addition, only costs incurred within hospital admissions were considered, further studies will be required to evaluate the total medical and social costs of NAFLD.

5. Conclusions

Patients diagnosed with NAFLD/NASH and attended in Catalan hospitals displayed a significant level of comorbidity, with a disease complexity that is likely to correlate

with a more intensive use of medical resources and costs. Promoting measures to increase the early detection of NAFLD/NASH could contribute in reducing the level of comorbidity of this patient population and, as a consequence, the associated medical costs. Overall, this study provides data to inform resource allocation and disease management decisions at the regional level, which should take into account the high proportion of patients with multiple chronic conditions.

6. Transparency section

6.1. Data Availability Statement

The data that support the findings of this study is available upon request to the Catalan Institute of Health via ethics committee approval, yet data sharing is restricted due to legal stipulations. Requests must be addressed to the Health Evaluation and Quality Agency of Catalonia (AQuAS) http://aquas.gencat.cat/en/inici/.

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8. Tables

Table 1 Baseline characteristics of patients diagnosed with non-alcoholic fatty liver disease (NAFLD).

	Total	< 60 years	≥ 60 < 80 years	≥ 80 years
Admission files, N	150,236	30,359	74,424	45,453
Individual patients, N	24,172	4997	11,386	7789
Male patients, %	60.0	72.5	66.5	42.5
In-hospital mortality rate, % (95% CI)	31.2 (30.6-31.8)	24.5 (23.3-25.7)	29.5 (28.6-30.3)	38.1 (37.0-39.2)
Charlson Comorbidity Index (CCI) (95% CI)	5.1 (5.1-5.1)	4.2 (4.1-4.2)	5.0 (4.9-5.0)	5.9 (5.9-5.9)
Secondary conditions registered upon admission:	-	-	-	-
Cirrhosis of liver without mention of alcohol	36.2	32.8	32.3	45.0
Essential hypertension	25.6	10.6	26.4	34.7
Type II diabetes mellitus	21.2	10.4	24.0	24.3
Ascites	18.1	20.5	18.0	16.6
Portal hypertension	17.7	21.4	18.3	14.3
Secondary esophageal varices without bleeding	13.8	15.2	14.4	12.0
Hepatocellular carcinoma	12.9	7.3	12.9	16.2
Hepatic encephalopathy	10.7	9.6	11.1	10.9
Iron deficiency anemia, unspecified	9.3	7.1	8.9	11.8
Personal history of tobacco use	8.7	6.3	10.8	7.6
Unspecified atrial fibrillation	8.7	1.1	7.4	16.2
Acute kidney failure, unspecified	8.3	6.6	8.3	9.5
Hyperlipidemia, unspecified	8.0	4.3	9.5	8.3
Urinary tract infection, site not specified	6.8	4.3	6.2	9.4
Congestive heart failure, unspecified	6.1	1.4	5.2	10.7

Chronic kidney disease, unspecified	6.0	2.7	5.7	9.0
Calculus of gallbladder without cholecystitis without obstruction	4.6	4.9	4.5	4.8
History of liver replaced by transplant	4.6	5.9	6.1	1.3
Acute respiratory failure	4.6	4.6	4.2	5.2
Isolated steatosis	4.4	3.6	4.5	4.8

Table 2 Conditions associated to in-hospital mortality in patients diagnosed with non-alcoholic fatty liver disease (NAFLD).

	Non deceased patients (95% CI)	Deceased patients (95% CI)	p-value ¶
Charlson Comorbidity Index (CCI) (95% CI)	5.1 (5.1-5.1)	6.0 (6.0-6.1)	p<0.0001
Cirrhosis of liver without mention of alcohol	35.2 (35.0-35.5)	56.1 (54.9-57.2)	p<0.0001
Essential hypertension	26.0 (25.8-26.3)	19.1 (18.2-20.0)	p<0.0001
Type II diabetes mellitus	21.6 (21.4-21.8)	16.2 (15.4-17.1)	p<0.0001
Ascites	17.3 (17.1-17.5)	33.3 (32.3-34.4)	p<0.0001
Hepatocellular carcinoma	12.5 (12.3-12.6)	20.1 (19.2-21.1)	p<0.0001
Hepatic encephalopathy	9.7 (9.6-9.9)	29.1 (28.1-30.2)	p<0.0001
Iron deficiency anemia, unspecified	9.5 (9.3-9.6)	8.4 (7.8-9.0)	p=0.0012
Personal history of tobacco use	9.1 (9.0-9.3)	5.7 (5.2-6.3)	p<0.0001
Unspecified atrial fibrillation	8.6 (8.5-8.8)	11.3 (10.6-12.1)	p<0.0001
Acute kidney failure, unspecified	7.1 (6.9-7.2)	32.4 (31.3-33.4)	p<0.0001
Urinary tract infection, site not specified	6.7 (6.5-6.8)	10.6 (9.9-11.3)	p<0.0001
Congestive heart failure, unspecified	5.9 (5.8-6.0)	9.7 (9.1-10.4)	p<0.0001
Chronic kidney disease, unspecified	5.9 (5.8-6.0)	9.5 (8.8-10.1)	p<0.0001
Calculus of gallbladder without cholecystitis without obstruction	4.7 (4.6-4.8)	3.8 (3.4-4.3)	P=0.0003
History of liver replaced by transplant	4.7 (4.6-4.8)	2.4 (2.1-2.8)	p<0.0001
Acute respiratory failure	3.5 (3.4-3.6)	24.1 (23.2-25.1)	p<0.0001
Isolated steatosis	4.5 (4.4-4.6)	2.1 (1.8-2.5)	p<0.0001

¶ p-value, deceased vs. non-deceased patients. CI: Confidence interval.

Table 3 Adjusted morbidity groups (GMA) according to number of chronic diseases and into 5 levels of complexity or risk in patients diagnosed with non-alcoholic fatty liver disease (NAFLD).

	Level 1, N (%)	Level 2, N (%)	Level 3, N (%)	Level 4, N (%)	Level 5, N (%)	Total, N (%)
Chronic disease (1 system)	12 (1.4)	25 (0.6)	10 (0.2)	17 (0.2)	16 (0.2)	80 (0.3)
Chronic disease (2 or 3 systems)	19 (2.2)	153 (3.5)	248 (4.9)	326 (4.5)	292 (4.5)	1038 (4.3)
Chronic disease (4 or more systems)	728 (86.0)	3651 (82.6)	3973 (78.1)	5946 (81.3)	5086 (78.2)	19,384 (80.2)
Active neoplasm	88 (10.4)	589 (13.3)	857 (16.8)	1026 (14.0)	1110 (17.1)	3670 (15.2)
Total	847 (3.5)	4418 (18.3)	5088 (21.0)	7315 (30.3)	6504 (26.9)	24,172 (100.0)

Table 4 Admission details and medical procedures registered during the admission of patients diagnosed with non-alcoholic fatty liver disease (NAFLD).

Hospital	Total (N=150,236)	< 60 years (N=30,359)	≥ 60 < 80 years (N=74,424)	≥ 80 years (N=45,453)
Urgent admissions, %	59.1	60.5	56.0	63.1
Scheduled admissions, %	40.9	39.5	44.0	36.9
Medical procedures:	-	-	-	-
Diagnostic echography	21.8	25.9	22.1	18.7
Computed tomography of head and thorax and abdomen	16.3	18.7	16.4	14.4
Routine chest x-ray	5.1	4.7	4.9	5.8
Electrocardiogram	4.1	3.0	3.9	5.1
Arteriography, angiography	3.7	2.9	4.0	3.7
Magnetic Resonance Imaging (MRI)	3.4	4.4	3.6	2.6
Abdomen x-ray	1.3	1.4	1.3	1.4
Microscopic examination	5.7	5.2	5.4	6.5
Circulatory monitoring	4.8	5.7	5.1	3.6
Non-surgical intubation and irrigation	5.7	7.7	7.7	3.5
Blood transfusion	13.8	14.8	14.8	13.0
Hemodialysis	1.3	1.4	1.6	0.9
Antibiotic injection	7.9	9.0	7.8	7.3
Injection or infusion of another therapeutic or prophylactic substance	6.7	6.2	6.6	7.1
Another injection of therapeutic substance into the liver	2.1	1.0	2.0	2.9
Injection or infusion of chemotherapy	2.3	1.3	2.3	2.9
Liver biopsy	4.1	5.8	4.8	1.7
Other biopsies	1.4	1.3	1.5	1.3
Percutaneous abdominal drainage (paracentesis)	14.0	15.7	14.1	12.9
Bowel incision, removal, and anastomosis	7.1	7.1	7.1	7.2
Operations over the thoracic wall, pleura and diaphragm	2.1	2.2	2.1	2.1
Local excision or removal (destruction) of lesion or tissue of the esophagus	9.0	12.6	9.2	6.3

Partial hepatectomy or destruction of lesions	1.7	1.0	1.8	2.1
Liver transplant	0.9	1.5	1.1	0.013
Physiotherapy	5.5	5.3	5.3	6.1

CI: Confidence interval.

Table 5 Mean annual cost of hospital care per age group.

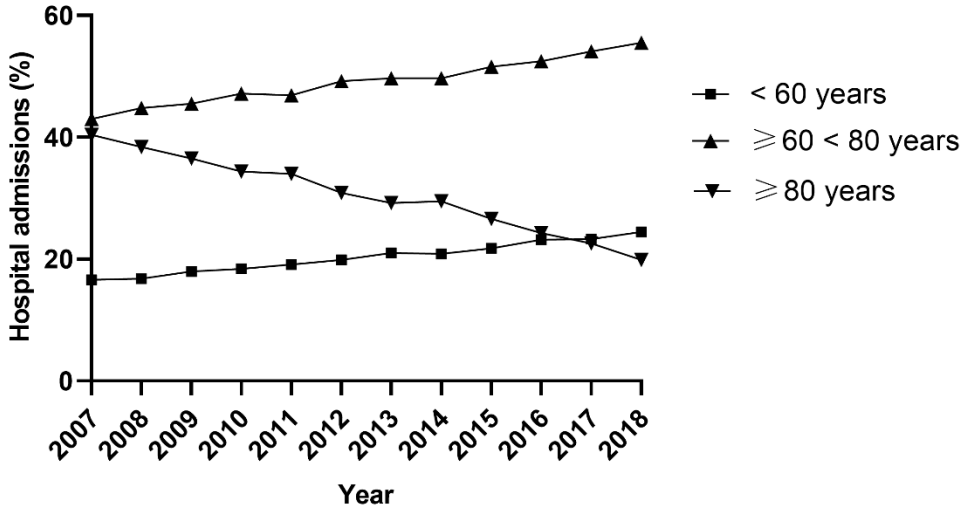
	Total (N=150,236)	< 60 years (N=30,359)	≥ 60 < 80 years (N=74,424)	≥ 80 years (N=45,453)
Diagnostic imaging procedures	€1,097,691	€197,546	€574,803	€325,343
Microscopic examination of sample	€3885	€720	€1,821	€1345
Monitoring of vitals	€78,910	€18,931	€42,189	€17,790
Non-surgical intubation, irrigation	€45,967	€12,143	€25,102	€8722
Blood transfusion	€499,553	€106,694	€246,421	€146,438
Hemodialysis	€32,016	€6,944	€18,832	€6240
Injection of therapeutic substance (excluding chemotherapy)	€1,139,180	€223,009	€551,094	€365,077
Injection of chemotherapy	€2,015,760	€232,656	€1,006,400	€776,704
Surgical procedures: Diagnostic (biopsies)	€2,202,602	€103,245	€1,017,483	€1,081,875
Surgical procedures: Therapeutic (excision of lesions, hepatectomy…)	€14,429,336	€3,307,303	€7,324,745	€3,797,288
Surgical procedures: Liver transplant	€5,712,080	€1,940,219	€3,743,537	€28,324
Other cancer treatment (hyperthermia)	€1183	€123	€563	€497
Physiotherapy and rehabilitation	€112,664	€21,531	€52,459	€38,674
Total annual cost	€27,370,827	€6,171,062	€14,605,448	€6,594,138

CI: Confidence interval.

9. Figures

Figure 1 (A) Percentage of hospital admissions per age groups registered by year and (B) in-hospital mortality rate per age groups by year (2007-2018).

A.



B.

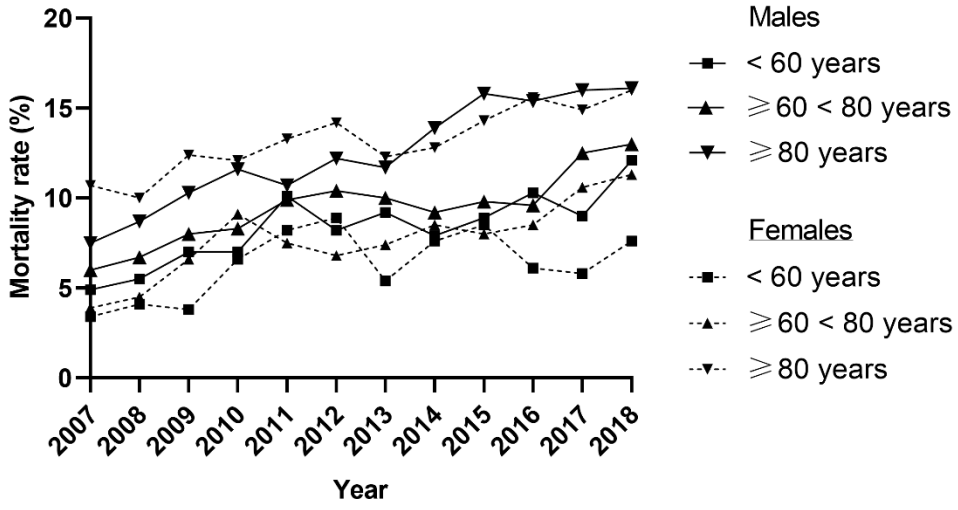


Figure 2 Disease complexity levels associated to risk in the general population (A) and in patients diagnosed with non-alcoholic fatty liver disease (NAFLD) (B).

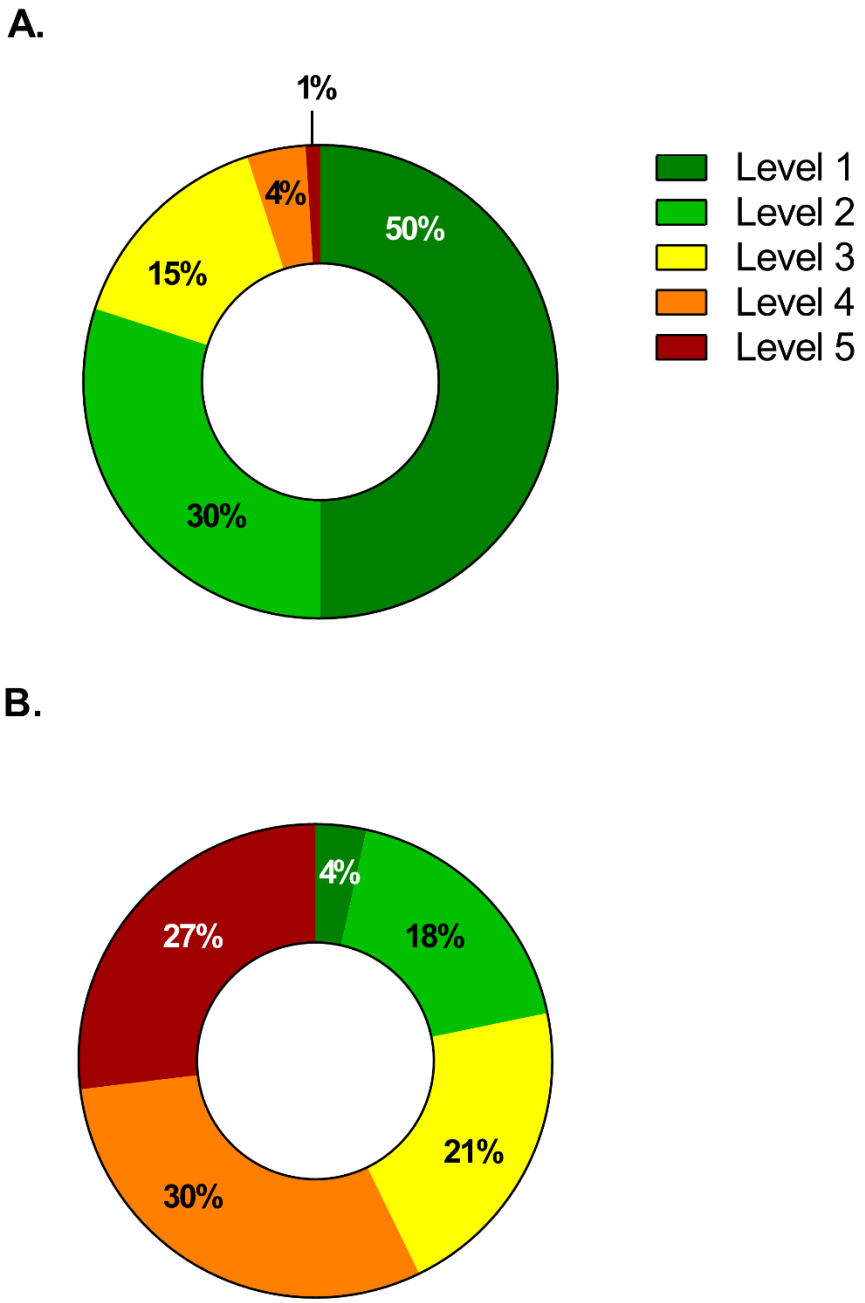
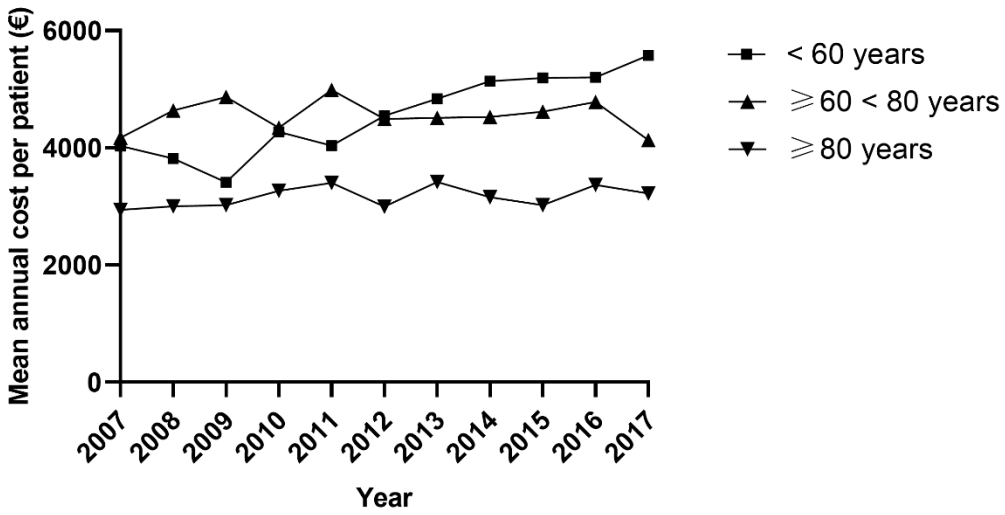


Figure 3 (A) Mean annual cost per patient by year and (B) total annual cost (2007-2017).

A.



B.