ORIGINAL PAPERS

Overall clinical and economic impact of non-alcoholic fatty liver disease

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ABSTRACT

Objectives: to establish the clinical and economic consequences (resource utilization and healthcare costs) of non-alcoholic fatty liver in the setting of the usual clinical practice in Spain.

Patients and methods: an observational, retrospective study was performed based on a review of the medical records of adult patients ≥ 18 years of age who sought medical care from 2017 to 2018. Patients were categorized into two groups according to fibrosis stage (estimation method: FIB-4): a) F0-F2; and b) F3-F4 (advanced fibrosis). Follow-up lasted one year. Primary endpoints included comorbidity, concomitant medication, resource utilization and costs. Results were analyzed using a multivariate approach with $p < 0.05$.

Results: a total of 8,151 patients were recruited with a mean age of 61.1 years and 51.5 % were male. By group: a) mild fibrosis n = 7,127, 87.4 %; and b) advanced fibrosis n = 1,024, 12.6 % (6.8 % with liver cirrhosis). The most common comorbidities included 63 % dyslipidemia, 52 % obesity, 52 % hypertension and 35 % diabetes. The average number of drugs used was 2.1 per patient. Patients with advanced fibrosis (F3-F4) had a higher average number of concomitant medications (2.5 *vs* 2.1; $p < 0.001$) and a higher AST/ALT ratio (1.1 *vs* 0.8; $p < 0.001$). The average cost (patient-year) for subjects with advanced fibrosis, corrected for covariates, was higher (€1,812 *vs* €1,128, $p < 0.001$). Age, morbidity, concomitant medication, fibrosis stage and total costs were higher in patients with diabetes.

Conclusions: patients with advanced fibrosis were associated with more comorbidity and concomitant medications, which resulted in higher healthcare costs for the National Health System.

Keywords: Fatty liver. Non-alcoholic. Liver fibrosis. Resource utilization. Costs.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease with an estimated prevalence of 20-30 %, which varies according to country and ethnic group (1-3). It occurs as the result of multiple factors such as being overweight, central obesity, dyslipidemia, insulin resistance and diabetes. All of which are associated with metabolic syndrome. In this respect, the condition has been currently redesignated as metabolic associated fatty liver disease (MAFLD). An increase in incidence is expected over the next few years (4,5).

The course of NAFLD encompasses a spectrum of disease ranging from simple steatosis to non-alcoholic steatohepatitis (NASH) and/or liver fibrosis, which may predispose

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to developing cirrhosis and hepatocellular carcinoma over time. In general, it is associated with the presence of cardiovascular events (CVEs) (6,7). Presently, no drug therapy has been accepted for NAFLD, although several agents have been used. Recommended medications include vitamin E (PIVENS study [9]), pioglitazone (NASH plus diabetes) and statins (NASH plus dyslipidemia), according to the American Association for the Study of Liver Disease (AASLD) (10). Multiple drugs are now being studied as potential therapeutic agents (9-11).

Prevention, early detection and fostering a healthy lifestyle must be the most cost-effective measures for reducing the incidence, prevalence and progression of the disease. This may bring about clinical improvement (metabolic control goals) and a reduction in the use of healthcare resources (2-13). Establishing fibrosis extent is key in these patients. To achieving this, alternatives to traditional liver biopsy are available, including imaging techniques (ultrasound, transient elastography, shear wave elastography, etc.) and serum markers. Methods predictive of liver fibrosis, developed from biochemical/serological laboratory parameters obtained in the clinical practice (NAFLD fibrosis score, AST-to-platelet ratio index [APRI], FIB-4, BARD score [BMI, AST/ALT ratio, diabetes mellitus], FibroTest, Hepamet Fibrosis Score, etc.) are also available (14,15).

Some studies have shown that the presence of fibrosis, especially degrees F3-F4, triggers a faster disease progression, with increased morbidity and mortality in these patients. Furthermore, clinical data (fibrosis degree, impact of disease) and economic data related to NAFLD are scarce in Spain. The goal of the study was to establish the clinical and economic consequences of NAFLD in the usual clinical practice in Spain. Specific goals included: a) estimating the clinical impact of NAFLD according to fibrosis extent (F0-F2/F3-F4); b) describing the demographic characteristics, associated comorbidities and concomitant medications (polymedication) of the participants; and c) evaluating the economic impact on resource use and associated healthcare costs, both in general and among diabetic individuals.

PATIENTS AND METHODS

Study design and population

An observational, multicenter, longitudinal, retrospective study was performed based on a review of medical records (computer databases with dissociated data *[patient identification not allowed]*). The study population was obtained from healthcare records at several Spanish Primary Care and specialist care centers (hospitals) (unified in the dissociated, anonymized BIG-PAC® database, Real Life Data; http://www.encepp.eu). Data were collected from electronic medical records and supplementary funding/public service provision databases in seven Spanish autonomous communities (1.8 million patients). Information on data sources remained confidential.

Inclusion and exclusion criteria

Patients were assessed who sought care from 01/01/2017 to 31/12/2017 and had the following characteristics: a) age ≥ 18 years; b) diagnosed with NAFLD (ICD-9/ICD-10); and c) capable of undergoing regular follow-up (≥ 2 healthcare records in the electronic system). Patients were excluded when: a) transferred to another center or relocated outside the healthcare area; b) permanently institutionalized; and/or c) diagnosed with another conditions (viral hepatitis, chronic alcoholism, Wilson's disease, autoimmune disorders, celiac disease, and/or hemochromatosis, end-stage disease and/or dialysis).

Study groups and follow-up

According to the degree of fibrosis, patients were categorized into two groups: a) F0-F2; and b) F3-F4 (advanced fibrosis). Fibrosis grade was measured using the FIB-4 (16) estimation method (age, ALT, AST and platelets; FIB-4 index = [age (years) × AST (IU/l)] / [platelet count (10^9/l) × ALT (IU/l)]$^{1/2}$). Patients were followed up for one year.

Disease definition and fibrosis grade

NAFLD criteria used were from the International Classification of Diseases (ICD-10-CM: codes K75.8, K76.0; and/or ICD-9-MC: code 571.8). Furthermore, NAFLD diagnosis was confirmed with some imaging test or histology. The cut-off value for patient inclusion in the advanced fibrosis group was FIB-4 > 3.25 points, in order to achieve a higher predictive value for advanced fibrosis (16).

Sociodemographic and comorbidity variables

Sociodemographic and comorbidity variables were as follows: age (continuous at index date and by range), gender, time from diagnosis (years) and body mass index (BMI, kg/m^2), as well history of various diseases. The following was used for each patient as an overall comorbidity summary variable: a) Charlson's comorbidity index (17) as an approach to case severity; and b) number of chronic comorbidities. These variables were obtained at study onset (according to ICD-10-CM, ICD-9-CM codes). The presence of liver cirrhosis, cancer or transplant was also assessed.

Concomitant medication

Medication data were obtained from the Anatomical Therapeutic Chemical Classification System (ATC) (18). Drugs for specific patients were selected at the discretion of the attending physician (clinical practice). Information was collected from the medication dispensing records. The following concomitant medications were obtained, per therapeutic group: hypotensive agents, diuretics, lipid-lowering agents, antidiabetic drugs, anxyolithics/antidepressants, and analgesic/anti-inflammatory drugs.

Resource utilization and costs

Healthcare costs (direct costs) associated with healthcare activities by professionals (doctor visits, hospitalization days, emergencies, diagnostic or therapeutic orders, and pharmacy prescriptions) were detailed, as were non-healthcare (indirect) costs related to work productivity losses

Table 1. *Detailed unit costs and work productivity losses (year 2018)*

Healthcare and other resources	Unit costs (€)
Doctor visits	
Primary Care	23.19
Hospital Emergency Room	117.53
Specialist care*	92.00
Hospitalization (one day's stay)	420.90
Diagnostic tests	
Laboratory tests	22.30
Conventional radiology	18.50
Other diagnostic/therapeutic tests	67.12
Computed tomography	92.00
Magnetic resonance imaging	154.00
Other tests	37.12
Pharmacy prescription	RP-VAT
Work productivity-Indirect costs	
Cost per day of sick leave	101.21

Source of healthcare resources: proprietary analytical cost accounting and Spanish National Statistics Institute (INE). Values expressed in euros. RP: retail price. *Only in Endocrinology, Gastroenterology and Internal Medicine departments.

(days on sick leave). Cost was expressed as the mean cost per patient (average/unit) throughout the study period. Study items and their economic assessment are detailed in table 1 (for year 2018). Rates were obtained from site analytical accounting records, except for medication and sick leave days. Prescriptions were quantified according to per-box retail prices at the time of prescription (as per the Bot Plus, *Consejo General de Colegios de Farmacéuticos Oficiales de España*). Sick leave days or productivity losses were considered as non-healthcare costs (indirect costs, related to the national average salary) (source: Spanish National Statistics Institute [INE]) (19).

Information confidentiality/ethical aspects

The study was registered by the Spanish Agency of Medicines and Medical Devices (AEMPS) (EPA-OD) and subsequently approved by the ERB of Hospital de Terrassa.

Statistical analysis

Database search terms were taken from data processing sentences (SQL script). Data were carefully reviewed using an exploratory analysis and then prepared for statistical analysis, recording their frequency distributions and looking for potential errors in their recording or coding (20). A univariate descriptive analysis was performed with 95 % confidence intervals for parameter estimations. For the bivariate analysis the ANCOVA, Pearson's linear correlation and Chi-squared tests were used. An analysis of covariance (ANCOVA; estimated marginal means; Bonferroni's adjustment) was performed to correct for healthcare/non-healthcare costs. Covariates included: gender, age, overall comorbidity and time from diagnosis. Furthermore, a binary logistic regression model was constructed to establish which variables were associated with advanced fibrosis (procedure: enter; statistic: Wald test). The SPSS-WIN version 23 program was used and statistical significance was set at $p < 0.05$. A sub-analysis of healthcare costs was performed for the following scenarios: a) cut-off at FIB-4 > 2.67 points for patient inclusion in the advanced fibrosis group; b) patients with liver cirrhosis; and c) per comorbidity extent (Charlson's index: 1, 2 or 3+).

RESULTS

From an initial selection of 802,635 adult subjects, 8,151 patients (NAFLD) who met the study inclusion criteria were enrolled (Fig. 1). A total of 12.6 % (n = 1,024; 95 % CI: 11.9-13.3 %) were diagnosed with advanced fibrosis (F3-F4) (6.8 % with liver cirrhosis). All patients had a confirmed diagnosis of NAFLD and the FIB-4 score calculated.

Table 2 shows the baseline characteristics of the study series by study group. The mean age was 61.1 (SD: 13.3) years and 51.5 % were male. Patients with advanced fibrosis (F3-F4) were older (66.3 *vs* 60.3 years; $p < 0.001$) and had more comorbidities (2.5 *vs* 1.8 points; $p < 0.001$) and the presence of cardiovascular risk factors was the most prominent. The average medication was 2.1 (SD: 1.6), with 41.7 % hypotensive agents and 41.4 % lipid-lowering drugs. Patients with advanced fibrosis (F3-F4) had a higher average number of concomitant medications (2.5 *vs* 2.1; $p < 0.001$), FIB-4 score (5.2 *vs* 1.6; $p < 0.001$) and AST/ALT ratio (1.1 *vs* 0.8; $p < 0.001$) (Table 2). The diagnostic tests that were used in patients with advanced fibrosis included: 99.8 % liver ultrasound, 32.6 % computed tomography, 24.2 % magnetic resonance imaging, 18.8 % transient elastography (TE) and 13.8 % liver biopsy. Testing included in F0-F2patients was: 100 % liver ultrasound and 22.3 % other diagnostic modalities.

Table 3 shows the use of resources and associated costs (in EUR) by study group. The total cost (n = 8,151) amounted to €9.9 million, of which 91.2 % corresponded to healthcare (direct) costs and 8.8 % to non-healthcare costs (productivity loss). The yearly average/unit cost for subjects with advanced fibrosis corrected for covariates (ANCOVA) was higher (€1,812 *vs* €1,128, $p < 0.001$; difference: €684). These differences persisted for healthcare costs (€1,727 *vs* €1.019, $p < 0.001$; difference: €708) whereas no conclusive differences in work productivity losses were obtained (€84 *vs* €109, $p = 0.254$; difference: €-25). Patients with diabetes were older and had a greater burden of morbidity, concomitant medication, fibrosis grade and total costs (€1,546 *vs* €1,037); $p < 0.001$.

In the logistic model, diabetes (OR = 2.8; 95 % CI: 2.4-3.2), obesity (OR = 1.5; 95 % CI: 1.3-1.7), blood hypertension (OR = 1.1; 95 % CI: 1.0-1.1) and age (OR = 1.1; 95 % CI: 1.0-1.2) were associated with advanced fibrosis ($p < 0.002$ for all variables). Sub-analyses revealed the following healthcare costs: a) FIB-4 cut-off > 2.67 (patients in the advanced fibrosis group [n = 1,033, 12.8 %] had higher costs [€1,933 *vs* €983; $p < 0.001$, respectively]); b) patients with liver cirrhosis (n = 155; €2,724); and c) according to Charlson's index: 1: €776, 2: €1,258, 3+: €1,996 ($p < 0.001$). Liver fibrosis extent (FIB-4) showed a moderate correlation with healthcare cost ($r = 0.384$, $p > 0.001$). Total cost (ANCOVA) for patients with

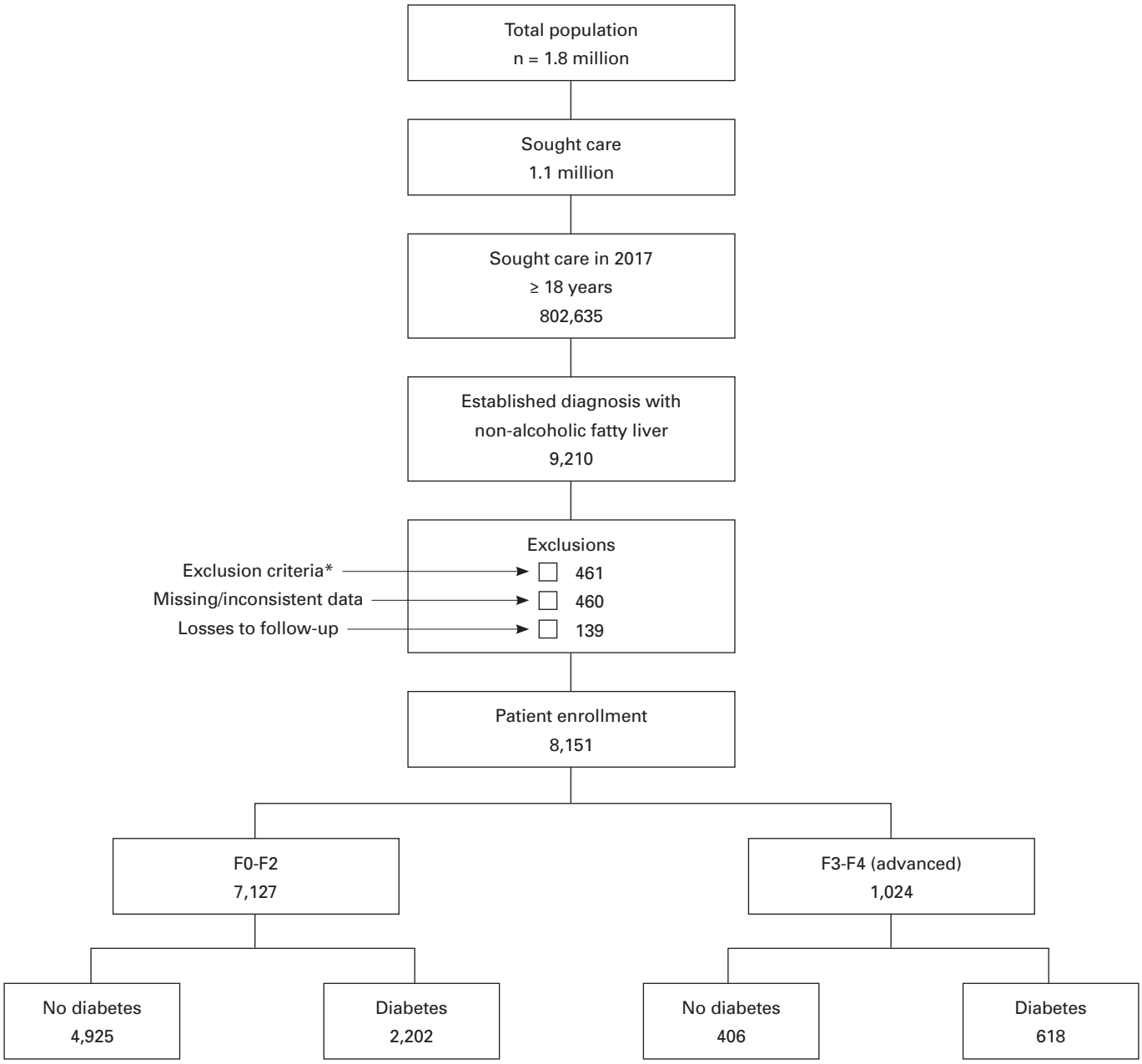

Fig. 1. *General study diagram. *Exclusion criteria, n = 461: transferred/relocated (150), institutionalized (97), viral hepatitis (108), chronic alcoholism (15), Wilson's disease (5), autoimmune diseases (14), celiac disease (21), hemochromatosis (3), end-stage disease and/or dialysis (48).*

advanced fibrosis (excluding patients with liver cirrhosis) *vs* F0-F2 remained higher (€1,776 *vs* €1,128; p < 0.001).

DISCUSSION

The study results show that patients with advanced fibrosis were associated with higher levels of comorbidity and concomitant medication. Hence, there was a higher healthcare cost for the National Health System. A total of 8,152 patients diagnosed with NAFLD were enrolled. The prevalence of non-alcoholic fatty liver as diagnosed using ultrasound varies between 17-46 % among the general population and 60-80 % in the at-risk populations (21). Disease under-recording is obvious in our series, as revealed by the disagreement between coded data and the results obtained from epidemiological studies. In this regard, the high prevalence of NAFLD, the need to differentiate between levels of liver involvement extent, the failure to assess severity with ultrasound and the diagnostic limitations of biopsy all prompt a search for non-invasive approaches to facilitate diagnosis and assess disease progression (8,13). In this respect, all indirect, non-invasive modalities combining biochemical markers and clinical parameters easily collectable in the daily clinical practice are of interest (2,12,13).

Several serologic indices are available to assess fibrosis extent. The NAFLD Fibrosis Score (NFS), Hepamet Fibrosis Score (HFS) and FIB-4 are the most commonly validated in the literature (22).

Table 2. *Baseline characteristics (demography, morbidity), concomitant medication and biochemical parameters by study group*

Study group Number of patients, %	F0-F2 n = 7,127 (87.4 %)	F3-F4 n = 1,024 (12.6 %)	Total n = 8,151 (100 %)	p
Sociodemographic characteristics				
Average age, years	60.3 (13.1)	66.3 (13.4)	61.1 (13.3)	< 0.001
Gender (male)	51.7 %	49.5 %	51.5 %	0.181
General comorbidity				
Average diagnoses	3.2 (1.5)	4.0 (1.4)	3.3 (1.5)	< 0.001
Average Charlson index	1.8 (1.2)	2.5 (1.4)	1.9 (1.2)	< 0.001
Associated comorbidities				
Blood hypertension	50.6 %	61.8 %	52.0 %	< 0.001
Diabetes	30.9 %	60.4 %	34.6 %	< 0.001
Dyslipidemia	63.4 %	61.1 %	63.1 %	0.153
Obesity	50.0 %	63.2 %	51.7 %	< 0.001
Ischemic heart disease	6.7 %	10.7 %	7.2 %	< 0.001
Vascular cerebral accident	2.2 %	5.7 %	2.6 %	< 0.001
Heart failure	2.6 %	8.4 %	3.4 %	< 0.001
Renal failure	4.5 %	9.1 %	5.1 %	< 0.001
COPD	7.4 %	12.4 %	8.0 %	< 0.001
Depressive syndrome	9.6 %	14.4 %	10.2 %	< 0.001
Malignancies	5.2 %	8.4 %	5.6 %	< 0.001
Polycystic ovarian syndrome	0.3 %	0.5 %	0.4 %	0.445
Psoriasis	4.7 %	5.0 %	4.7 %	0.663
Hidradenitis	1.0 %	1.3 %	1.0 %	0.445
Osteoporosis	5.6 %	8.3 %	5.9 %	0.001
Liver cirrhosis	0.0 %	6.8 %	1.9 %	< 0.001
Liver cancer	0.0 %	1.5 %	0.4 %	< 0.001
Liver transplant	0.0 %	3.0 %	0.2 %	< 0.001
Concomitant medication				
Hypotensive drugs	40.7 %	48.5 %	41.7 %	< 0.001
Diuretics	10.0 %	19.8 %	11.2 %	< 0.001
Lipid-lowering agents	39.3 %	56.1 %	41.4 %	< 0.001
Antidiabetics	23.4 %	46.7 %	26.4 %	< 0.001
Anxiolytics/antidepressants	35.0 %	39.9 %	35.7 %	0.002
Painkillers	56.0 %	61.6 %	56.7 %	0.001
Average medications				
Mean (DE)	2.1 (1.6)	2.5 (1.7)	2.1 (1.6)	< 0.001
Median (P25-P75)	2.0 (1-3)	3.0 (1-4)	2.0 (1-3)	
Time from diagnosis, years				
Mean (SD)	4.2 (1.8)	6.5 (1.8)	4.8 (1.8)	< 0.001
Median (P25-P75)	4.1 (2.7-5.8)	4.5 (3.0-6.1)	4.1 (2.7-5.8)	
Body mass index, kg/m²				
Mean (SD)	32.3 (17.7)	32.5 (18.4)	32.1 (18.1)	0.114
Median (P25-P75)	31 (28-37)	31 (28-37)	31 (28-37)	
AST/ALT ratio				
Mean (SD)	0.8 (0.2)	1.1 (0.2)	0.9 (0.2)	< 0.001
Median (P25-P75)	0.8 (0.8-1.0)	1.0 (1.1-1.2)	0.9 (0.8-1.0)	
FIB-4				
Mean (SD)	1.6 (0.4)	5.2 (2.3)	2.0 (1.5)	< 0.001
Median (P25-P75)	1.6 (1.3-1.9)	4.5 (3.8-5.9)	1.7 (1.3-2.1)	

Values expressed as a percentage or mean (SD: standard deviation). p: statistical significance; COPD: chronic obstructive pulmonary disease; P: percentile; AST: aspartate aminotransferase; ALT: alanine aminotransferase; FIB-4: Fibrosis-4 score.

Table 3. *Resource utilization and associated costs (average/patient-year, in EUR) by study group*

Study groups Number of patients, %	F0-F2 n = 7,127 (87.4 %)	F3-F4 n = 1,024 (12.6 %)	Total n = 8,151 (100 %)	p
Primary Care visit	11.6 (12.1)	15.6 (16.5)	12.1 (12.8)	< 0.001
Laboratory tests	2.1 (2.1)	3.2 (2.6)	2.2 (2.2)	< 0.001
Conventional radiology	0.3 (0.5)	0.4 (0.6)	0.3 (0.6)	< 0.001
Computed tomography	0.2 (0.5)	0.3 (0.6)	0.2 (0.5)	< 0.001
Magnetic resonance imaging	0.1 (0.4)	0.3 (0.5)	0.1 (0.4)	< 0.001
Other diagnostic/therapeutic tests	0.1 (0.3)	0.1 (0.4)	0.1 (0.3)	< 0.001
Hospitalization (stays)	0.2 (1.5)	1.4 (4.1)	0.4 (2.0)	< 0.001
Specialist care visit	0.4 (1.1)	0.8 (1.2)	0.5 (1.1)	< 0.001
Emergency Room visits	0.1 (0.6)	0.3 (0.8)	0.1 (0.6)	< 0.001
Sick leave days	1.1 (8.9)	0.7 (5.6)	1.1 (8.5)	0.172
Gross costs				
Healthcare costs	981.4 (1,088.3)	1,958.9 (2,113.8)	1,104.2 (1,304.4)	< 0.001
Primary Care costs	840.7 (696.1)	1,247.6 (972.5)	891.8 (748.7)	< 0.001
Doctor visits	270.1 (280.5)	362.1 (382.6)	281.7 (296.8)	< 0.001
Laboratory tests	47.1 (46.7)	70.5 (57.8)	50.1 (48.8)	< 0.001
Conventional radiology	5.0 (10.1)	7.8 (11.7)	5.3 (10.4)	< 0.001
Computed tomography	16.7 (42.8)	28.6 (55.0)	18.2 (44.7)	< 0.001
Magnetic resonance imaging	20.3 (56.6)	39.1 (72.1)	22.6 (59.1)	< 0.001
Other diagnostic tests	2.0 (9.6)	5.3 (16.2)	2.4 (10.7)	< 0.001
Medications	479.4 (522.4)	734.3 (730.3)	511.5 (559.2)	< 0.001
Hospital care costs	140.7 (700.6)	711.2 (1,798.4)	212.3 (933.2)	< 0.001
Hospitalization days	85.6 (615.7)	602.2 (1,740.5)	150.5 (860.8)	< 0.001
Doctor visits	40.0 (97.2)	74.3 (112.8)	44.3 (99.9)	< 0.001
Emergencies	15.0 (67.7)	34.8 (94.2)	17.5 (71.9)	< 0.001
Non-healthcare costs (productivity)	111.7 (897.6)	72.3 (568.8)	106.8 (863.3)	0.172
Total costs	1,093.1 (1,467.0)	2,031.2 (2,197.6)	1,211.0 (1,607.6)	< 0.001
*Corrected costs**			*Difference*	
Healthcare costs	1,019	1,727	708	< 0.001
95 % CI	991-1,046	1,652-1,801		
Non-healthcare costs (productivity)	109	84	-25	0.254
95 % CI	89-129	30-138		
Total costs	1,128	1,812	684	< 0.001
95 % CI	1,093-1,164	1,716-1,907		

Values expressed as the mean (SD: standard deviation). p: statistical significance; CI: confidence interval. *Corrected for covariates (ANCOVA model: contrasts are based on paired comparisons between estimated marginal means).

Both indices are very useful to rule out the presence of advanced fibrosis (high negative predictive value), particularly among the general population or Primary Care patients. To our understanding they may be a screening resource, as a step before transient elastography, to exclude patients at lower risk of advanced fibrosis and reduce the number of diagnostic tests (22,23). These indices should be present among the lab test results of patients (fibrosis stage estimation) so that professionals can optimize indications (24).

In our study, 12.6 % of subjects had advanced fibrosis. The systematic review by Weiß (25) concluded that 14-27 % of the general population in developed countries have NAFLD,

whereas 10-20 % of cases progress to fibrosis. Araújo (26) and Bellentani (27) reported similar results and highlight the significant association between NAFLD and metabolic syndrome. Our results are similar to those reported by these authors. Importantly in this study, patients with advanced fibrosis had an AST/ALT ratio = 1.1. Although this ratio was not > 2, which might have suggested alcoholic liver disease to some extent, the influence of some chronic liver condition on cirrhosis stage or other non-measured factors may have played a role in this result.

The average cost (patient-year) for subjects with advanced fibrosis, corrected for covariates, was significantly higher (€1,812 *vs* €1,128). The dearth of literature available on the economic burden of this disease should be highlighted (14). However, predictions suggest that NAFLD costs will increase, primarily because of the influence of obesity, diabetes and metabolic syndrome, both in adults and children (2,8). Ghamar-Chehreh (28) estimated an average person-year cost of $2,521 and acknowledged that most of these patients have significant cardiovascular risk factors. The authors point out that approximate estimations of the yearly costs related to diagnosis and management may be obtained based on prevalence. Tanajewski (29), in a theoretical economic assessment study (Markov's model), concluded that an intensive intervention upon risk factors would be more effective than preventive care (£2,138 per quality of life-adjusted life years [QALY] gained). This model was more sensitive for patients with advanced fibrosis. The review by Younossi (2015) (30) concluded that the prevalence of NAFLD is on the rise among the general population (due to an increase in obesity) and that NAFLD is a slow, progressive disease. Based on five studies (difficult to compare because of methodological differences), the cost of disease ranged from $608 to $12,347 per person-year, with patients with advanced fibrosis being the most costly. Cost is related to patient comorbidity burden and the rates used for each cost component are higher than in the present study.

NAFLD will not progress towards more aggressive disease forms in the majority of patients. Nevertheless, we compared the cost for advanced fibrosis (€1,812) with that in other studies performed with the same methods, and obtained interesting results. For example, a recent study to estimate the healthcare resources involved in the management of severe chronic obstructive pulmonary disease (COPD) and its flare-ups found that these were €1,861-1,935 per person-year, with flare costs (hospital stay days) being the main component (31). However, another study to assess the economic burden of the brand-name pregabalin for the treatment of neuropathic pain and generalized anxiety disorder reported a cost of €1,500 and €1,528, respectively (hospitalization costs were also relevant) (32). These data confirm the high cost of NAFLD, particularly in the advanced fibrosis stage. Patients with diabetes were older, with a greater morbidity, concomitant medication, fibrosis extent and total cost. These results deserve special consideration as patients with diabetes are considered to be at a very high cardiovascular risk. Our results seem consistent with the reviewed literature (2,5,6,8).

The study limitations are consistent with those characteristic of observational, retrospective studies: a) disease under-recording; b) professional variability; c) disease heterogeneity; d) study variable assessment system; and e) bias in fibrosis classification (FIB-4). Possible inaccuracies in the coding of NAFLD diagnosis or the absence of a variable apt to influence final results (patient socioeconomic level, prescribed drug dosage evolution, concomitant medication collection) are all typical limitations in these studies. In our series there is an under-recording of NAFLD, possibly due to lack of *a priori* diagnostic confirmation (unidentified cases), diagnostic methods (ultrasound findings) or overlooked factors (lack of diagnostic coding, etc.). However, the percentage of advanced fibrosis should not differ considerably. Given the short period wherein help-seeking patients were selected, the study was not designed to ascertain the prevalence of disease. Furthermore, the use of liver ultrasonography as a diagnostic criterion for NAFLD also involves a limitation since it may only identify NAFLD in patients with fatty infiltration of at least 25 %. Notwithstanding, the use of a liver biopsy as a diagnostic criterion would increase drop-outs and patient selection bias (24,33). It should be mentioned that ultrasounds may diagnose steatosis but not fibrosis, which is where the major impact of the condition resides. This issue highlights the importance of including fibrosis scores for the assessment of the population at risk (6,10,24). A major limitation of the study involves the measurement of NAFLD economic impact, as it was assessed jointly with the metabolic syndrome accompanying the condition. Therefore, in some cases in the mild NAFLD and the advanced fibrosis groups, cost components (Primary Care visits, medication, etc.) were counted that were not necessarily attributable to the disease alone but rather to patient comorbidities.

Implementing some non-invasive method for predicting liver fibrosis in the clinical practice may be of incalculable help for patient monitoring over time. To conclude, patients with advanced fibrosis were associated with greater comorbidity and concomitant medication levels, which resulted in higher healthcare costs for the National Health System. Further studies are needed to validate the consistency of our results.

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