ORIGINAL PAPERS

Analysis of the burden and variability in the management of NAFLD patients in the clinical practice: unifying the required criteria

Yolanda Sánchez-Torrijos[1], Javier Ampuero[1,2,3], Domingo Pérez Palacios[1], Rocío Gallego-Durán and Manuel Romero-Gómez[1,2,3]

[1]Clinical Management of Digestive Diseases Unit and CIBERehd. Hospital Universitario Virgen del Rocío. Sevilla, Spain. [2]Universidad de Sevilla. Sevilla, Spain. [3]Institute of Biomedicine of Seville. Seville, Spain

Received: 11/12/2018 · **Accepted:** 20/01/2018

Correspondence: Javier Ampuero and Manuel Romero-Gómez. Digestive Disease Department and CIBERehd. Hospital Universitario Virgen del Rocío. Av. Manuel Siurot, s/n. 41013 Sevilla, Spain. **e-mail:** jampuero-ibis@us.es; mromerogomez@us.es

ABSTRACT

Aim: to assess the prevalence of non-alcoholic fatty liver disease (NAFLD) in the gastroenterology outpatient clinic and describe the use of the resources accordingly.

Methods: a prospective and observational study of 403 patients seen in the gastroenterology outpatient clinic to rule out liver disease during three randomized months in 2016. The overall prevalence of NAFLD, disease severity, heterogeneity of the final diagnosis, the use of medical resources and their respective cost were analyzed.

Results: the main reason for consultation was hypertransaminasemia (42.9%, 173/403), followed by hepatitis C virus (HCV) (28.5%, 115/403). NAFLD was identified as the definitive diagnosis in 29.8% (120/403) of the cohort, 69.2% (83/120) derived by hypertransaminasemia and 24.2% (29/120) by steatosis. Laboratory tests were performed in 96.7% (116/120), abdominal ultrasound in 88.3% (106/120), viral serology in 79.2% (95/120) and autoimmunity in 70% (84/120) of patients with NAFLD. Liver fibrosis was not assessed in 87.5% of cases. In a post-hoc analysis, 12.1% (17/120) had advanced fibrosis by FIB-4. On ultrasound, 65% (73/106) had hepatic steatosis and 15% (17/106) chronic liver disease (significant fibrosis). The mean time for diagnosis was 2.23 ± 0.8 visits. The terminology used to define the clinical diagnosis was heterogeneous as follows: a) 48.3% (58/120) hepatic steatosis; b) 15% (18/120) non-alcoholic steatohepatitis; c) 15.8% (19/120) fatty liver; d) 13.3% (16/120) metabolic syndrome; and e) 7.5% (9/120) dual liver disease (fatty liver and alcohol). A pharmacological intervention was performed in six patients, a liver biopsy in two patients and another six were referred to another specialist. The average cost per patient until diagnosis was €570.78, which included analytical, autoantibodies, viral serology and abdominal ultrasound, with a mean of 2.5 consultations. Thus, the total expense in patients with NAFLD was €68,493.6.

Conclusion: NAFLD is a frequent cause of hypertransaminasemia. However, the heterogeneity in the management and terminology of the disease makes it necessary to initiate medical training actions in order to unify the criteria for disease control.

Key words: Non-alcoholic fatty liver disease. Non-alcoholic steatohepatitis.

INTRODUCTION

The number of patients referred to the gastroenterology outpatient clinic due to a suspicion of liver disease (i.e., steatosis, positive antibodies for hepatitis C virus [HCV] or hepatitis B virus [HBV], impairments in liver-related laboratory parameters, etc.) is increasing over time. In addition, neither the suitability of the derivation nor the derived costs have been extensively assessed. In this scenario, the adequate management of non-alcoholic fatty liver disease (NAFLD) could play a relevant role due to its increased prevalence over the last years. This is especially true in Western countries (1,2) and specifically in Spain (3). In fact, it has been calculated that up to 30% of the overall population has NAFLD, representing up to 70% in patients with comorbidities such as type 2 diabetes mellitus (4).

NAFLD ranges from steatosis or non-alcoholic steatohepatitis (NASH) to cirrhosis in the absence of alcohol consumption (5) and it is associated with metabolic risk factors such as obesity, dyslipidemia and diabetes (6,7). Despite the high prevalence of NAFLD, the vast majority of patients have simple steatosis, which is a benign condition and a small percentage have NASH or liver fibrosis. In fact, the latter is

Sánchez-Torrijos Y, Ampuero J, Pérez Palacios D, Gallego-Durán R, Romero-Gómez M. Analysis of the burden and variability in the management of NAFLD patients in the clinical practice: unifying the required criteria. Rev Esp Enferm Dig 2019;111(4):270-274.

DOI: 10.17235/reed.2019.6088/2018

associated with a progression of fibrosis by up to 80% (8). In addition to the obvious liver-related issues, NAFLD also influences the occurrence of cardiovascular diseases and represents the leading cause of mortality in patients with NASH and mild fibrosis. In patients with cirrhosis, the cause is liver-related (9,10).

Given the relevance of NAFLD in terms of persons affected and the potential consequences of achieving suitable derivations, this study aimed to determine the proportion of NAFLD patients seen in outpatient clinics. In addition, the variability in the diagnostic and therapeutic decision making was also assessed in order to implement adequate strategies to manage these patients.

METHODS

Study design and patients

This was an observational study and patients seen in the gastroenterology outpatient clinics to rule out the presence of liver disease were prospectively included during a randomized three month period in 2016. All patients who attended the outpatient clinic, apart from the following individuals were included: a) referred for liver transplant assessment; b) involved in clinical trials; c) already followed-up due to a liver disease; d) attended after a hospital discharge; and e) a suspicion of biliary disease. The study was approved by the Ethics Committee of our hospital after evaluation.

Patients without intermediate or advanced fibrosis (present F0-F1) were not considered to need follow-up in hepatology consultations, as they do not need specific management. Therefore, they can be reviewed by their primary care physician with periodic assessment of liver fibrosis.

Clinical end-points

The different causes of the derivations were collected in order to determine the overall prevalence of the different liver diseases, as well as the final diagnosis. In addition, an in-depth analysis of patients finally diagnosed with NAFLD was performed, evaluating the severity of the disease (by biochemical assessment of liver fibrosis such as FIB4: F0-F1 [FIB4 < 1.30], F3-F4 [FIB4 > 2.67]) (11), the variety of the terminology used to define the liver disease, the use of medical resources and their respective costs. All of these analyses were stratified according to the referral (i.e., primary care *versus* specialized care).

Cost analysis

The costs derived from the consultation and the different diagnostic tests performed were obtained from the official website of the Andalusian Health Service (http://www.juntadeandalucia.es/servicioandaluzdesalud/ordenpreciospublicos/):

- Laboratory parameters: €103.85
- Autoantibodies (ANA, ANCA, AML, antiLKM, AMA): €262.31
- Viral serology (hepatitis A virus [HAV], HBV, HCV): €97.44
- Abdominal ultrasound: €36.92
- First digestive consultation: €43.50
- Successive digestive consultation review: €17.84

Statistical analysis

The statistical package IBM SPSS version 21.0 was used. In order to characterize qualitative variables, tables of frequency distribution and percentages were performed. For the quantitative type, the statistics of centralization and dispersion were calculated (mean ± standard deviation). The sample size was not calculated because the aim was to collect all the patients who visited the outpatient office during the pre-specified time.

RESULTS

The main reason for consultation was hypertransaminasemia (42.9%, 173/403), followed by positive HCV antibody (28.5%, 115/403). The rest of the causes are shown in figure 1.

Causes of derivation depending on the origin of the referral

Most of the patients were referred from primary care units (52.9%, 213/403). Hypertransaminasemia was the main reason for consultation (57.7%, 123/213) and HCV was the main reason in specialized care (38.9%; 74/190). With regard to the final diagnosis, NAFLD (37.6%, 80/213) was the predominant cause in patients derived from primary care and HCV (39.5%; 75/190) from other specialized units. The clinic discharge of patients referred from primary care (24.4% [52/213]) was two times more frequent than specialized care (13.7% [26/190]). Taking into account the patients discharged, NAFLD was the most frequent diagnosis (67.3% [35/52] *vs* 34.6% [9/26]) in both cases.

Prevalence and management of NAFLD

NAFLD was identified as the definitive diagnosis in 29.8% (120/403) of the total cohort (Fig. 2); hypertransaminasemia in 69.2% (83/120) and steatosis in 24.2% (29/120) were the main reasons for the derivation. The general characteristics are described in table 1. It should be noted that in the consultation, body mass index (BMI) was calculated in 37 of the 120 patients.

The tests required to reach the final diagnosis are detailed in table 2. The mean time for diagnosis was 2.23 ± 0.8 visits. The most commonly used imaging technique was ultrasound (93%; 106/120), steatosis was identified in 65% (73/106) and signs of chronic liver disease, in 15% (17/106). With regard to laboratory parameters, hypertransaminasemia (predominantly higher levels of alanine aminotransferase [ALT]), altered glycated hemoglobin and high total cholesterol (Table 3) were observed. Liver biopsy was performed in two patients to confirm the definitive diagnosis. Five patients were referred to another specialist, three to Endocrinology, one to Nephrology

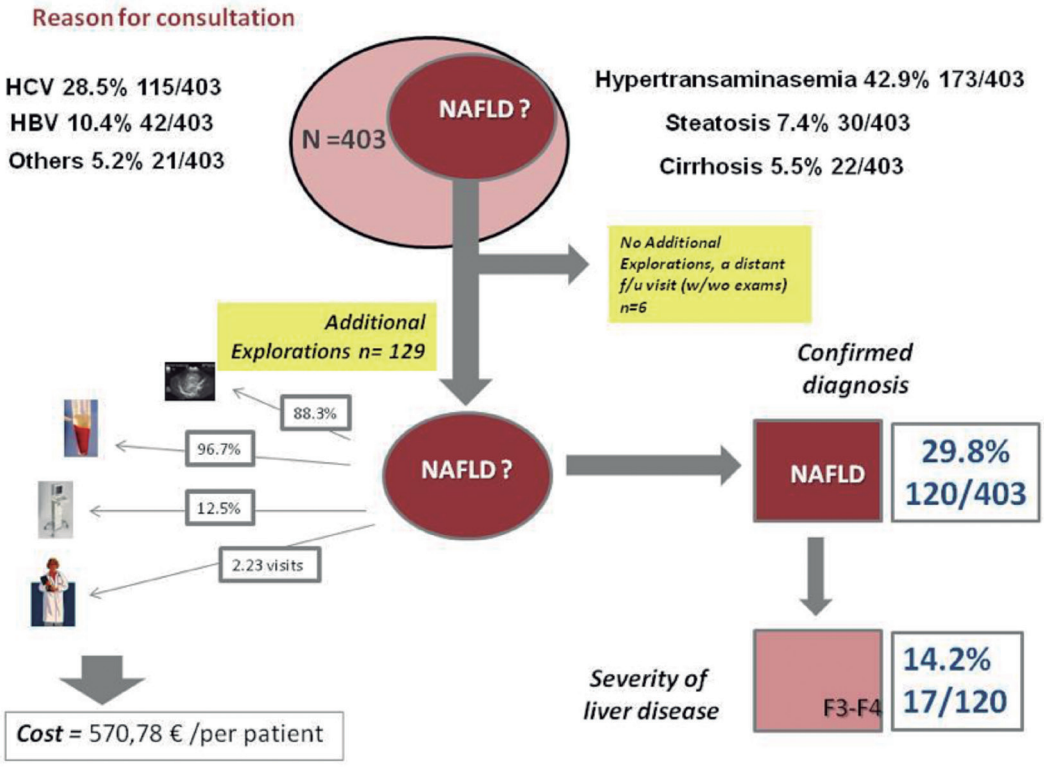

Fig. 1. *Flow diagram of the care process. The main reasons for consultation are presented, as well as the subsequent tests that the patients underwent to reach the final diagnosis (HCV: hepatitis C virus; HBV: hepatitis B virus; NAFLD: non-alcoholic fatty liver disease).*

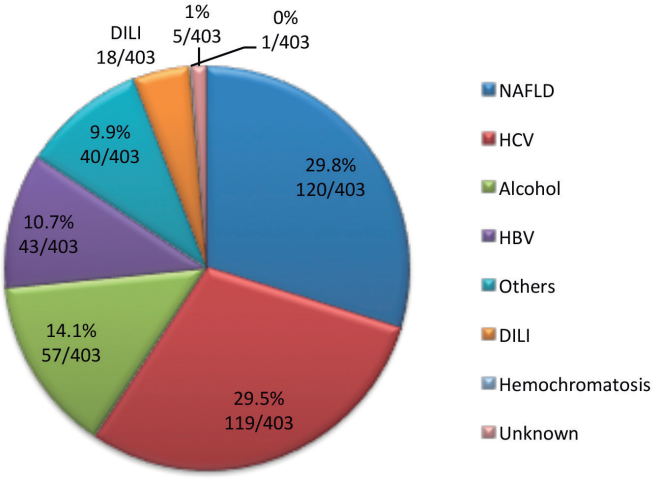

Fig. 2. *Final diagnosis. Final diagnosis after the study in consultation (NAFLD: non-alcoholic fatty liver disease; HCV: hepatitis C virus; HBV: hepatitis B virus; DILI: drug-induced liver injury).*

Table 1. *General characteristics of NAFLD patients*

Age (years old)	53.56 ± 15.19
Sex (males)	60% (72/120)
Body mass index (kg/m^2)	30.96 ± 5.37
Primary care	66.7% (80/120)
Obesity	28.3% (34/120)
Diabetes	26.7% (32/120)
Dyslipidemia	60.8% (73/120)
Discharge	36.7% (44/120)

and another to a cardiovascular risk unit. Furthermore, six patients started a pharmacological intervention, including simvastatin (n = 3), fenofibrate (n = 2) and ursodeoxycholic acid (n = 1). Finally, 36.7% (44/120) of NAFLD patients were discharged from the gastroenterology outpatient clinic.

The severity of the disease was evaluated by non-invasive fibrosis tests (FIB4) in a post-hoc analysis and 12.1% (17/120) had advanced fibrosis (Fig. 3). With regard to patients without advanced fibrosis (n = 73), fewer than a half of subjects were discharged (41.1% [30/73]).

Terminology used for NAFLD

The terminology used to define the clinical diagnosis of NAFLD was heterogeneous as follows: a) 48.3% (58/120) hepatic steatosis; b) 15% (18/120) non-alcoholic steatohepatitis; c) 15.8% (19/120) fatty liver; d) 13.3% (16/120) metabolic syndrome; and e) 7.5% (9/120) dual liver disease (fatty liver and moderate chronic alcoholism < 50 g per day). Furthermore, 17.2% (10/58) of patients diagnosed due to hepatic steatosis had a normal abdominal ultrasound.

Table 2. *Diagnostic tests*

Diagnostic tests	NAFLD
Blood test	116/120 (96.7%)
Autoantibodies (ANA, ANCA, SMA, anti-LKM, AMA)*	84/120 (70%)
Viral serology (HCV, HBV)†	95/120 (79.2%)
Image tests	106/120 (88.3%)
2nd image tests‡ (CT/MR)	4/120 (3.6%)
Transient elastometry	15/120 (12.5%)
NAFLD fibrosis score	4/120 (3.3%)
FIB 4	3/120 (2.5%)

The number of patients to whom each test is performed is represented. *ANA: antinuclear antibodies; ANCA: anti-neutrophil cytoplasmic antibodies; SMA: smooth muscle antibodies; AMA: anti-mitochondrial antibodies; †HCV: hepatitis C virus; HBV: hepatitis B virus; ‡CT: computerized tomography; MR: magnetic resonance.

Table 3. *Lab test of NAFLD patients*

Analytical values (mean ± standard deviation)	
ALT	62 ± 32 mU/ml
AST	47 ± 27 mU/ml
GGT	213 ± 330 mU/ml
Glucose	142.75 ± 73.46 mg/dl
Glycated hemoglobin	8.3 ± 3.2%
Total cholesterol	235 ± 50 mg/dl
LDL	153 ± 61 mg/dl
HDL	53 ± 26 mg/dl
Triglycerides	208 ± 165 mg/dl
Ferritine	450 ± 512 µg/l
Platelets	210000 ± 167

ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gammaglutamiltransferase; LDL: low density lipoprotein; HDL: high density lipoprotein.

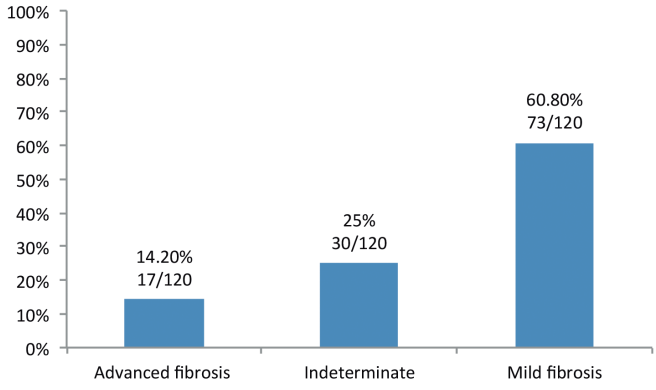

Fig. 3. *Degree of fibrosis according to FIB4 in NAFLD patients.*

Costs from the healthcare of NAFLD patients

The costs derived from the healthcare of NAFLD patients are shown in table 3. The average cost per patient was €570.78, taking into account: a) a general lab test (renal, hepatic and lipid profiles, proteinogram, total blood count, coagulation and iron metabolism), autoantibodies, hepatotropic virus serology and abdominal ultrasound; and b) an average of 2.5 consultations. Thus, the overall cost would be €68,493.6 for the total number of patients with NAFLD (n = 120). The costs derived from an inadequate referral (73 patients showing FIB-4 < 1.30) were €41,666.94, which represented 60.8% of total costs.

DISCUSSION

Despite the fact that the number of patients referred from primary and specialized care to gastroenterology outpatient clinics was very similar (52.9% *vs* 47.1%), the reason for referral varied. We found that hypertransaminasemia predominated in primary care, which is similar to other studies (12) and HCV was more frequent in specialized care. This was probably due to the greater number of serologies performed at that level. Accordingly, the final diagnosis was more frequently HCV infection in specialized care, as expected. However, NAFLD was more frequent in primary care, which indicates the growing volume of NAFLD patients usually managed by the primary care physicians. Regarding the overall cohort, both NAFLD and HCV had a similar prevalence.

A quarter (25%) of the patients derived from primary care were discharged, which represented more than double of those from specialized care. NAFLD was the most frequent diagnosis at discharge in these individuals, defined by abdominal ultrasound and/or biochemical criteria, in the absence of another liver disease (13). Interestingly, many of these patients had mild fibrosis (61%) according to a post-hoc FIB4. Despite this, less than a half of them were discharged. Other non-invasive methods for fibrosis assessment were not performed, such as transient elastography, which are considered as determinants for the management of the severity of the disease (14). Perhaps NAFLD patients without advanced fibrosis by blood-based non-invasive tests could be managed in primary care centers with annual assessments and therefore, do not require follow-up in specialized consultations (15). Consequently, there could be savings of up to 60% in the healthcare costs from the derivation of NAFLD patients when those with mild fibrosis are avoided. Only the direct costs of the public institution were taken into account, since the indirect costs such as loss of days worked, transport and patient anxiety are hardly tangible, despite their importance from a social perspective.

The terminology used to define NAFLD clinically was very heterogeneous, including hepatic steatosis, fatty liver, non-alcoholic steatohepatitis, or metabolic-related liver disease. Interestingly, the diagnosis of non-alcoholic steatohepatitis is histological (4), even though it was used without a liver biopsy. In addition, almost 20% of patients were diagnosed with steatosis with a normal abdominal ultrasound. It is essential to use accurate clinical terms to standardize the diagnosis, especially in patients without a liver biopsy (16).

In addition to the usual intervention of lifestyle, such as promoting a Mediterranean diet, the abandonment of sedentarism and moderate aerobic exercise (17,18), six patients received a pharmacological treatment of simvastatin, ursodeoxycholic acid and fenofibrate. None of these are currently recommended as a treatment for NAFLD (4,19). It is also remarkable that only five patients were referred to another specialist, including Endocrinology, Nephrology and Cardiology, despite the presence of baseline metabolic risk factors such as obesity, dyslipidemia and diabetes. Perhaps NAFLD patients should be integrated more frequently into multidisciplinary teams to ensure the adequate control of the liver-related and other unrelated risks (20).

NAFLD is a frequent cause of derivation, especially from primary care centers, and represents a growing volume of healthcare resources. Consequently, it is essential to determine adequate criteria for derivation and optimal management of the disease, particularly assessing the presence of advanced liver fibrosis to avoid unnecessary referrals. The heterogeneity of the clinical terms used to define NAFLD and the different management of the disease in specialized units make it necessary to implement informative actions to unify the criteria used in patient management.

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