

ORIGINAL PAPERS

Usefulness of an index score as a predictor of hepatic fibrosis in obese patients undergoing bariatric surgery

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ABSTRACT

Objective: to evaluate the usefulness of a non-invasive clinical score to predict liver fibrosis in the steatosis associated with morbid obesity.

Patients and methods: we included 88 patients, who underwent bariatric surgery in the Sanitary Area of León, Spain, and who showed a liver biopsy with steatosis greater than 5%. This is a retrospective study in which the rate of fibrosis is calculated from tests performed during the preoperative period, and is then compared to data from intraoperative hepatic biopsies. The analysis population was grouped according to the presence of advanced fibrosis in the liver biopsy (grade 3-4) or its absence (grade 0-2). The cutoff used for diagnosing advanced fibrosis was 0.676 (high cutoff point), and the cutoff point to exclude advanced fibrosis was -1.455 (low cutoff).

Results: the prevalence of advanced fibrosis in the histological samples was 5.5%, and 65.9% of patients had no fibrosis. The cutoff for a low negative predictive value was 100%, and sensitivity was 100%. The cutoff point for a high positive predictive value was 1.7%, and specificity was 31.3%.

Conclusions: this scoring system for morbidly obese patients eligible for bariatric surgery allows to identify those without advanced fibrosis, but cannot predict who may have advanced fibrosis

Key words: Morbid obesity. Non-alcoholic fatty liver disease. Fibrosis.

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INTRODUCTION

Obesity in Spain is a health problem with a prevalence around 15% in the adult population (1). Obesity can cause complications at various levels in the human body, the liver being one of the organs most commonly affected.

The liver is affected in the form of non-alcoholic fatty liver, an entity that includes a spectrum of diseases ranging from simple steatosis to cirrhosis. The prevalence of steatosis and non-alcoholic steatohepatitis in obese patients undergoing bariatric surgery is 91 and 32%, respectively (2).

Milder forms of liver damage may progress to more advanced forms. It has been estimated that approximately 53% of patients with steatosis remain stable, while 32% progress towards steatohepatitis, of whom 7-16% progress to cirrhosis (3,4).

Bariatric surgery may be a treatment for fatty liver disease because it improves insulin resistance, which is a pathogenic factor (5,6). It is indicated in those patients who have a BMI greater than 40 or higher than 35 with comorbidities, according to the consensus of the Spanish Society for the Study of Obesity (SEEDO) (7). Multiple studies with paired liver biopsies (during and after surgery) have shown improved liver histology after weight loss surgery (8-10).

Liver biopsy is the gold standard method for establishing the diagnosis and prognosis of non-alcoholic fatty liver. It is an invasive method with associated morbidity (0.3%) and mortality (0.01%) (11), and has certain limitations such as intra- and inter-observer variability, and its ability to only analyze a small portion of liver tissue (1:50.000) (12). Because of these limitations liver biopsy is not deemed a diagnostic method applicable to the general population.

Given the potential progression of non-alcoholic fatty liver to advanced fibrosis, a less invasive diagnostic

method to identify patients with advanced fibrosis earlier, so they are subjected to monitoring and complications of cirrhosis are prevented, has been sought.

In this regard, and given the impossibility of generalizing biopsy as a diagnostic method, various scores have been developed with clinical and/or laboratory data (13,14). Among the scores published in the literature the proposal by Angulo et al. can be highlighted (15). This scoring system was developed and validated in a population with a high prevalence of advanced liver fibrosis, and showed a suitable diagnostic yield.

The aim of this study was to verify the clinical utility of the scoring system proposed by Angulo et al. (15) for the detection of hepatic fibrosis in obese patients with fatty liver who are candidates to bariatric surgery.

PATIENTS AND METHODS

Patients

This is a retrospective study conducted in a third-level hospital. Patients eligible for bariatric surgery were selected in an endocrine clinic according to SEEDO consensus criteria (7).

One hundred and twenty-one patients with morbid obesity in the health area of León, operated between July 1999 and August 2007, were selected. Of these 121 patients, 33 with steatosis smaller than 5% were excluded, so the study was finally conducted on 88 patients (Fig. 1).

Routine lab tests were performed for all patients before surgery, with the purpose of excluding other causes of liver damage (hepatitis B, hepatitis C, iron profile, immune markers). No patients showed pathological alcohol consumption or used potentially hepatotoxic drugs (methotrexate, tetracyclines, high doses of estrogen or steroids). The procedure was carried out by the same surgical team, who performed a Scopinaro's biliopancreatic diversion.

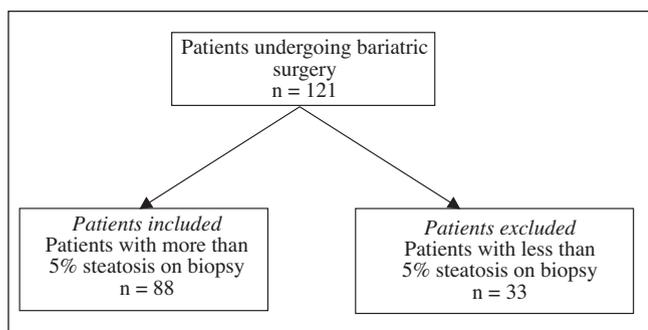


Fig. 1. Classification of patients analyzed in the study.
Clasificación de los pacientes analizados en el estudio.

Histological study

Two biopsies of the right liver lobe using a Tru-cut needle were taken early during the procedure to avoid possible changes in liver histology associated with the intervention. The consent for biopsy was collected with the consent for surgery.

The analysis of the biopsy was performed by a single group of pathologists. Steatosis was classified as minimal (1-5%), mild (6-33%), moderate (34-66%), or severe (67-100%) (16).

Fibrosis was classified according to the National Institutes of Health-sponsored NASH Clinical Research Network guidelines: 1) slight fibrosis in zone 3 or portal fibrosis or moderate fibrosis in zone 3; 2) fibrosis in zone 3 and the portal area; 3) bridging fibrosis; and 4) cirrhosis.

In our study, patients were grouped according to the findings of histology in non-advanced fibrosis (0-2) versus advanced fibrosis (3-4). This division was made with the aim of identifying patients with advanced fibrosis, as these would be those who would benefit from liver biopsy and regular monitoring to prevent cirrhotic complications.

Preoperative assessment

Laboratory data (fasting glucose, GOT, GPT, albumin, and platelets) were obtained in the preoperative workup.

The criteria of the American Diabetes Association (ADA) were used for the diagnosis of diabetes: two fasting glycemicias over 126 mg/dl, or randomly collected glucose levels above 200 mg/dl. Hyperglycemia was diagnosed for patients with a baseline fasting blood glucose greater than 100 mg/dl (17).

NAFLD fibrosis score was calculated using the formula described by Angulo et al. (15): $0.037 + -1.675 * \text{Age (years)} + 0.094 * \text{BMI (kg/m}^2) + 1.13 * \text{Hyperglycemia or DM (yes = 1, no = 0)} + 0.99 * \text{GOT / GPT} - 0.013 * \text{Platelets (x10}^9/\text{L)} - 0.66 * \text{Albumin (g/dl)}$.

Statistical analysis

Data were collected using Microsoft Excel 2003, and analyzed using SPSS (SPSS, Chicago, IL, USA; V13.0 for Windows). Continuous variables are expressed as mean (standard deviation) values and categorical variables as absolute numbers or percentages. Variables that showed no significance with the Kolmogorov-Smirnov test were considered normal and analyzed for comparisons using Student's t-test for independent variables and ANOVA. Categorical variables were analyzed using the Chi-squared test and Fisher's exact test when necessary. Significance was considered for a p value < 0.05.

The calculated values for sensitivity, specificity, and positive and negative predictive values took into account

the upper and lower cutoffs calculated by Angulo et al. (15). The upper cutoff used for diagnosing advanced fibrosis was 0.676 after applying the formula. The lower cutoff used to exclude advanced fibrosis was a result less than -1.455 after applying the formula.

RESULTS

Characteristics of the population

The population included in the study had a mean age of 40.6 years (11.3), and a body mass index (BMI) of 52.7 kg/m² (8.2). The mean values of GOT and GPT were 24.3 (14.9) and 34.3 (28.8) units/liter. Average platelet count was 268,000 (63,500) x 10⁹/L, and albumin 4.1 (0.3) g/dl. Table I describes the distribution of groups per histological data. The prevalence of advanced fibrosis was 5.5%.

Table I. Distribution of steatosis and fibrosis in the study patients

Mild steatosis	51.6%
Moderate steatosis	33%
Severe steatosis	15.4%
Without fibrosis	65.9%
Fibrosis grade 1	18.7%
Fibrosis grade 2	9.9%
Fibrosis grade 3	4.4%
Fibrosis grade 4	1.1%

Analysis of fibrosis prediction using the formula and comparing the results with those of liver biopsy

On applying the formula (with the cutoff points proposed), 42.4% of patients are in the indeterminate group (the value obtained by applying the formula is between two points).

Patients were divided into two groups, one with advanced fibrosis (grade 3 and 4), n = 5, and one without advanced fibrosis (grade 0 - 2), n = 83; values obtained

with the formula were compared. Patients with advanced fibrosis had a significantly higher score than patients without advanced fibrosis (fibrosis scores - advanced vs. non-advanced, p = 0.0028). After including the cutoff points proposed by Angulo et al. (15) in a ROC curve analysis, the area under the curve obtained was 0.0776, revealing a limited diagnostic utility.

On applying the formula, 20 patients (24.09%) were classified in the group of non-advanced fibrosis, none of these had advanced fibrosis on their biopsy (negative predictive value 100% and sensitivity 100%); 58 patients were classified according to the formula in the group of advanced fibrosis, only 1 of these had advanced fibrosis on the biopsy (positive predictive value of 1.7%, specificity 31.3%) (Table II).

From a total of 88 patients, 21 (23.9%) were correctly classified. We analyzed the diagnostic performance of other cutoffs, and none of them showed better results than those reported by Angulo et al. (15).

DISCUSSION

This study has several limitations. First, the study was based on a population with a particular age and body mass index, so the results cannot be extrapolated to the general obese population. Second, the index was developed on a population with features that do not match those of the population in this study. Third, although it was used for histological classification criteria by the same group of pathologists, there is probably some degree of intra- and inter-observer variability in sample classification.

Due to the high prevalence of non-alcoholic fatty liver, many scores are designed to improve the diagnosis of fibrosis. Many of them include parameters not available in clinical laboratories (aminoterminal propeptide of type III collagen, or tissue inhibitor of metalloproteinase 1, hyaluronic acid, endothelin 1, etc.) (13,18,19), which limits their use in clinical practice. With our improved understanding of the pathogenesis of the disease apoptosis markers have been proposed (cytokeratin 18 as a result of caspase 3) to play a role in the differential diagnosis between steatohepatitis and non-alcoholic steatosis (20).

Table II. Comparison of the results after applying the formula to patients in Hospital de León, with the results obtained by Angulo et al. (15) (in the group of patients used for design and validation) and Qureshi (22)

		Qureshi (22)	Angulo: estimation group (15)	Angulo: validation group (15)	Hospital of León
High cutoff	NPV	98%	93%	88%	100%
	Sensitivity	96%	82%	77%	100%
Low cutoff	PPV	33%	90%	82%	1.7%
	Specificity	84%	98%	96%	31.3%

Fibroscan has been recently introduced as a non-invasive method for diagnosing liver fibrosis in patients with non-alcoholic fatty liver (21). The results are encouraging because they get to a level of F3 and F4 fibrosis, an area under the curve increased (0.9). More studies are needed to validate its usefulness in patients with non-alcoholic fatty liver disease.

The system proposed by Angulo et al. (15) is a noninvasive method for the diagnosis of fibrosis. The parameters included in the formula are routinely analyzed in routine clinical practice. It was designed by a multicenter study in 480 patients, and was validated on 253. In total, 27% of patients in this study showed advanced fibrosis, while 33.3% did not show fibrosis.

This score was applied afterwards by Qureshi et al. (22) on 331 morbid obesity subjects who underwent bariatric surgery; 36.5% of patients had no fibrosis, and 13.6% had advanced fibrosis. Unlike the series, the results presented here show 65.9% of patients suffering from fibrosis, while only 5.5% showed advanced fibrosis in the study (Table I).

Furthermore, the index was designed in a population with a mean age of 47.7 years and a mean BMI of 32.42 (kg/m²), while the average age of patients in our study was 41.2 and BMI was 52.7 (kg/m²). Qureshi et al. (22) show a mean age of 40.5 and BMI of 48.4 (kg/m²). The different values of BMI, although part of a formula, might have influenced validity in our group.

The data for the low cutoff are consistent with data published to date. In addition to the high cutoff point, the positive predictive value is very low when compared to other studies (Table II). The different values observed are probably due to a low prevalence of advanced fibrosis, since patients have different characteristics. As BMI increases in the population, a decrease in PPV and specificity for high cutoffs occurs.

The study published by Angulo et al. (15), for an estimated 5% prevalence of advanced fibrosis, found a positive predictive value for the high cutoff point of 64% (95% CI 53-75). A value much higher than that was obtained in this study. No other cutoffs had a better performance than that proposed by Angulo et al. (15).

On applying this index many patients are classified as indeterminate (42.4%), and only a small fraction of obese patients will benefit from this index. It cannot be assumed that patients with a score above the high cutoff point had advanced fibrosis.

It seems reasonable to apply this index to morbidly obese patients, given its ease of implementation, and given that those below the low cutoff will likely have no fibrosis (NPV 100%). A total of 22.7% of our population will benefit from this index.

More studies will be needed to validate this index in various populations of obese patients, and perhaps to change some of the parameters in the formula according to the different populations in order to improve its utility.

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