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Determination of the risk of liver fibrosis with the FIB-4 scale in 290,353 spanish workers: Associated variables

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Abstract

Objective: Liver fibrosis is a progressive disease characterised by the accumulation of excessive scar tissue in the liver. It occurs in response to chronic viral hepatitis, alcohol abuse or non-alcoholic fatty liver disease (NAFLD). There are different ways to diagnose it, including FIB-4. The aim of this study is to assess which variables are associated with increased liver fibrosis as determined by FIB-4.

Material and methods: A cross-sectional descriptive study of 290,353 Spanish workers, evaluating the influence of age, sex, social class, tobacco consumption, and BMI on the prevalence of hepatic fibrosis determined by FIB-4.

Results: The prevalence of moderate and high FIB-4 values is 12.8% in women and 4% in women. These prevalence increase with age, as socioeconomic status decreases, in smokers and as BMI increases.

Conclusion: The profile of a person with elevated FIB-4 values will be a male, older, with a low socioeconomic status, smoker and overweight.

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Introduction

Hepatic fibrosis is a pathological process representing the excessive accumulation of extracellular matrix (ECM) in the liver as a result of chronic injury. This accumulation occurs when the liver's repair mechanisms are imbalanced, leading to an excessive formation of fibrous connective tissue. Over time, hepatic fibrosis can progress to cirrhosis, the final stage of fibrosis, which is associated with a significant increase in morbidity and mortality (1).

Hepatic fibrosis is the result of a scarring response to chronic liver damage, characterized by the accumulation of collagen and other components of the ECM in the liver. Although it may initially be reversible, advanced fibrosis can culminate in cirrhosis, an irreversible condition that significantly alters the liver's architecture and compromises its function (2). Hepatic fibrosis develops through a dynamic process involving the activation of hepatic stellate cells, which are responsible for collagen production, as well as dysregulation of ECM homeostasis (3).

In its early stages, hepatic fibrosis is generally asymptomatic, making early diagnosis a challenge. As fibrosis progresses, patients may develop signs and symptoms related to liver dysfunction. The clinical manifestations vary depending on the severity and complications that arise as the disease advances. In early hepatic fibrosis, no specific symptoms may be present, but as cirrhosis develops, symptoms can include fatigue, jaundice, peripheral edema, ascites, and esophageal varices (4).

One of the clinical challenges is that the manifestations are not specific to fibrosis itself but rather to the underlying liver damage or cirrhosis. In advanced stages, patients may develop portal hypertension, leading to complications such as ascites and hepatic encephalopathy, as well as an increased risk of developing hepatocellular carcinoma (HCC) (5).

Hepatic fibrosis can have multiple etiologies, depending on the factors causing chronic liver damage. The most common causes include:

- Chronic viral hepatitis: Chronic infection with hepatitis B (HBV) and C (HCV) viruses is a major cause of hepatic fibrosis worldwide. Both viruses cause chronic liver inflammation which, if left untreated, can lead to fibrosis formation and progress to cirrhosis (6).
- Chronic alcoholism: Excessive alcohol consumption is another major cause of hepatic fibrosis. Oxidative damage and inflammation caused by alcohol activate hepatic stellate cells, leading to collagen production and fibrosis development (7).
- Non-alcoholic fatty liver disease (NAFLD): NAFLD is an increasingly prevalent condition associated with metabolic syndrome, obesity, type 2 diabetes, and dyslipidemia. In its more advanced form, NAFLD can progress to non-alcoholic steatohepatitis (NASH), which is associated with inflammation and fibrosis (8).
- Primary biliary cholangitis and primary sclerosing cholangitis: These autoimmune diseases affect the bile ducts and can cause chronic liver damage, leading to fibrosis and eventually cirrhosis (9).
- Other causes: Less common etiologies of hepatic fibrosis include hemochromatosis (a genetic disease that leads to iron accumulation in the liver), Wilson's disease (a copper metabolism disorder), and certain toxins and medications (10).

The diagnosis of hepatic fibrosis is crucial to prevent its progression to advanced stages like cirrhosis. However, detecting fibrosis in its early stages remains a challenge, as available non-invasive methods are not always accurate in the initial phases of the disease.

1. Liver biopsy

Traditionally, liver biopsy has been considered the "gold standard" for evaluating hepatic fibrosis. This procedure allows for a direct assessment of the degree of fibrosis and inflammatory activity in the liver tissue. However, it is an invasive procedure with risks such as bleeding and pain, and it is subject to sampling errors, which can lead to underestimation or overestimation of the fibrosis stage (11).

2. Non-invasive methods

In the past decade, several non-invasive methods have been developed to assess hepatic fibrosis, reducing the need for biopsies in many patients. The most commonly used methods include:

- Transient elastography (FibroScan®): This method measures liver stiffness using a special ultrasound technique. Liver stiffness correlates with the

degree of fibrosis, and this method has proven useful in identifying patients with significant fibrosis or cirrhosis (12).

- Serum fibrosis indices: Several serum markers and combinations of markers have been validated to estimate hepatic fibrosis. These include the Fibrosis-4 Index (FIB-4), the aspartate aminotransferase to platelet ratio index (APRI), and patented markers such as FibroTest® (13).
- Magnetic resonance elastography (MRE): MRE is a more recent technique that uses magnetic resonance imaging to assess liver stiffness, providing a more accurate assessment than transient elastography in some cases, although it is more expensive and less available (14).

3. Conventional imaging

Although not sensitive for early fibrosis detection, imaging techniques such as ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) can be useful in evaluating complications of advanced fibrosis, such as portal hypertension, ascites, and HCC (15).

The goal of this study is to assess how age, sex, social class, smoking, and BMI are associated with FIB-4 values.

Material and methods

A descriptive, cross-sectional study was performed in 342,942 (137,504 women 205,438 men) between January 2018 and December 2019. 2148 workers were previously excluded (173 did not agree to participate and 1973 lacked a variable to calculate FIB-4). Leaving 340,794 (136,645 women and 204,149 men). See flow chart in Figure 1.

Eligibility criteria

To participate in the study, one of the selection criteria was an age range between 18 and 69 years. Additional conditions included being employed by one of the companies involved in the research, signing an informed consent form, and agreeing to allow the data to be used for epidemiological purposes.

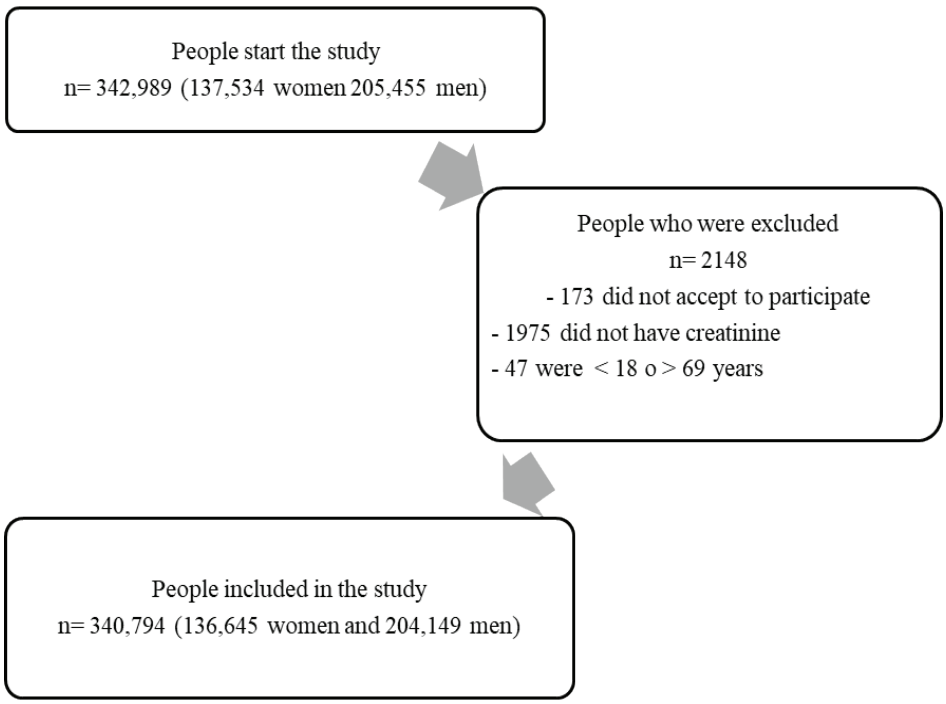

Figure 1: Flow chart of the study participants.

Variable assessment

Healthcare staff from the participating companies collected the necessary anthropometric and analytical data to calculate the FIB-4 index. The methods for measurement were standardized to reduce potential biases in data collection.

Measurements were taken while the participant stood upright with a relaxed abdomen. A SECA scale was used to record both height and weight. Blood pressure was assessed using an OMRON-M3 sphygmomanometer. After resting for ten minutes, three blood pressure readings were taken at one-minute intervals, and the average of these measurements was recorded.

After a fasting period of at least 12 hours, AST, platelet count, blood glucose, triglycerides, and total cholesterol were measured using various methods, including precipitation techniques to determine HDL cholesterol. LDL cholesterol was calculated with the Friedewald formula, which is valid for triglyceride levels below 400 mg/dL. All blood test results were reported in milligrams per deciliter (mg/dL).

Participants' gender was categorized as either male or female. Age was determined by subtracting the participant's birth date from the date of the medical exam.

To classify social class, the criteria established by the Spanish Society of Epidemiology (16) were applied, based on job types included in the 2011 National Classification of Occupations (CNO-11). Three categories were created:

Social Class I: Includes university-educated professionals, artists, athletes, and managers.

Social Class II: Comprises skilled self-employed workers and intermediate-level professionals.

Social Class III: Consists of unskilled laborers.

Participants were considered smokers if they had smoked at least once in the previous 30 days or had quit smoking within the past year.

Body Mass Index (BMI) is determined by dividing a person's weight (in kilograms) by the square of their height (in meters). It is categorized as follows: underweight (less than 18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and obese (30 kg/m^2 or higher).

FIB-4, an indicator of liver fibrosis, was calculated using the following formula: FIB4 = (age × AST) / (platelet count × √ALT)(17).

Ethical considerations

The study adhered to the 2013 Helsinki Declaration and all relevant ethical standards for research. Participants' privacy and anonymity were rigorously protected throughout the process. The study received approval from the Balearic Islands Research Ethics Committee (CEI-IB), with reference number IB 483/20.

All data collected were anonymized, with only the principal investigator having access to participants' identities. In accordance with Organic Law 3/2018, passed on December 5, 2018, participants retained the right to access, correct, delete, or oppose the processing of their personal data. This legislation also provides for the protection of digital rights.

Statistical analysis

To analyze quantitative data, Student's t-test was employed to calculate means and standard deviations. For categorical variables, the chi-square test was used to assess prevalence rates. Binomial logistic regression analysis was also performed, with odds ratios and 95% confidence intervals being calculated. Cut-off points to determine high values of FIB-4 were calculated using ROC curves and determining sensitivity, specificity and Youden index. All statistical analyses were carried out using SPSS version 29.0, and a p-value of less than 0.05 was deemed statistically significant for the purposes of this study.

Results

The 340,794 workers included in the study displayed the anthropometric, clinical, analytical, sociodemographic, tobacco use, and overweight/obesity data outlined in Table 1. The average age of the participants was slightly above 40 years. Across all variables, men exhibited less favorable values compared to women.

Men comprised 52.1% of the sample, while women represented 47.9%. The largest age group fell between 30 and 49 years. The majority of participants belonged to social class III. Smoking prevalence was 34.7% among men and 29.2% among women. Based on BMI criteria, 20.2% of men and 17.5% of women were classified as

obese.

Table 2 shows that mean FIB-4 values in both sexes increase with age, also with decreasing socio-economic status, in smokers and with increasing BMI. Mean FIB-4 values are higher in men when stratified by the different variables. In all cases the differences observed show statistical significance.

Table 3 shows the prevalence of the different FIB-4 values stratified according to the different variables and shows that high FIB-4 values increase with increasing age and with decreasing socio-economic status. This prevalence of elevated values is also higher in smokers and in overweight and especially obese people. In all cases the differences found show a high level of statistical significance ($p<0.001$).

The results of the multivariate analysis using multinomial logistic regression (table 4) show that all the variables analysed are associated with the occurrence of high FIB-4 values. Of these, the highest odss ratios were found for older age and male gender.

Figure 2 shows the results of the ROC curve. The BMI value that best predicts the occurrence of elevated FIB-4 values is 26.5 kg/m2. This cut-off point has a sensitivity of 61.7%, a specificity of 60.8% and a Youden index of 0.278.

Table 1: Characteristics of the population.

	Men n=177,570	Women n=112,783	
	Mean (SD)	**Mean (SD)**	**p-value**
Age (years)	41.0 (11.4)	40.1 (11.2)	<0.0001
Height (cm)	174.8 (7.0)	162.0 (6.5)	<0.0001
Weight (kg)	81.6 (15.2)	66.8 (14.5)	<0.0001
Body mass index (kg/m²)	26.7 (4.6)	25.5 (5.3)	<0.0001
Systolic blood pressure (mmHg)	130.0 (15.4)	119.2 (15.8)	<0.0001
Diastolic blood pressure (mmHg)	79.3 (10.9)	74.1 (10.3)	<0.0001
Total cholesterol (mg/dl)	192.3 (39.5)	189.5 (38.16)	<0.0001
HDL-cholesterol (mg/dl)	52.4 (12.8)	63.2 (15.2)	<0.0001
LDL-cholesterol (mg/dl)	120.2 (34.2)	113.1 (33.0)	<0.0001
Triglycerides (mg/dl)	123.2 (99.9)	89.0 (49.8)	<0.0001
Glycaemia (mg/dl)	94.1 (22.0)	88.5 (15.6)	<0.0001
ALT (U/L)	29.9 (19.2)	19.6 (12.9)	<0.0001
AST (U/L)	29.9 (18.9)	19.0 (12.7)	<0.0001
GGT (U/L)	35.8 (47.1)	20.4 (22.9)	<0.0001
Platelets (10^9/L)	234.7 (53.9)	258.0 (62.2)	<0.0001
	Percentage	**Percentage**	**p-value**
18-29 years	19.2	21.1	<0.0001
30-39 years	25.2	27.0	
40-49 years	29.9	29.4	
50-59 years	21.1	18.5	
60-69 years	4.6	4.0	
Social class I	3.9	5.8	<0.0001
Social class II	14.1	25.0	
Social class III	82.0	69.2	
Non-smokers	65.3	70.8	<0.0001
Smokers	34.7	29.2	
Underweight	1.2	3.5	<0.0001
Normal weight	38.2	51.6	
Overweight	40.5	27.4	
Obesity	20.2	17.5	

HDL-c High density lipoprotein-cholesterol. LDL-c Low density lipoprotein-cholesterol. AST Aspartate Aminotransferase . ALT Alanine Aminotransferase. GGT Gamma glutamil transpeptidase.
SD Standard deviation

Table 2: Mean values of FIB-4 scale according age, social class, tobacco consumption and body mass index by sex

	Men			Women		
FIB-4	**n**	**Mean (SD)**	**p-value**	**n**	**Mean (SD)**	**p-value**
18-29 years	34016	0.54 (0.24)	<0.0001	23767	0.40 (0.17)	<0.0001
30-39 years	44848	0.79 (0.32)		30419	0.57 (0.25)	
40-49 years	53032	1.04 (0.43)		33189	0.75 (0.31)	
50-59 years	37587	1.29 (0.6)		20921	1.01 (0.42)	
60-69 years	8087	1.49 (0.82)		4487	1.21 (0.57)	
Social class I	7024	1.00 (0.48)	<0.0001	6497	0.71 (0.36)	<0.0001
Social class II	25007	0.98 (0.47)		28247	0.71 (0.38)	
Social class III	145539	0.94 (0.53)		78039	0.69 (0.39)	
Non-smokers	115886	0.99 (0.52)	<0.0001	79796	0.71 (0.40)	<0.0001
Smokers	61684	0.88 (0.50)		32987	0.66 (0.37)	
Underweight	2063	0.62 (0.37)	<0.0001	3959	0.57 (0.34)	<0.0001
Normal weight	67771	0.81 (0.44)		58138	0.66 (0.36)	
Overweight	71842	1.01 (0.51)		30942	0.74 (0.41)	
Obesity	35894	1.13 (0.59)		19744	0.76 (0.42)	

FIB-4 FIBROSIS estimated with 4 simple elements. SD Standard deviation.

Table 3: Prevalence of values of FIB-4 scale according age, social class, tobacco consumption and body mass index by sex

			Men				Women		
FIB-4		**Normal**	**Intermediate**	**High**			**Normal**	**Intermediate**	**High**	
	n	**%**	**%**	**%**	**p-value**	**n**	**%**	**%**	**%**	**p-value**
18-29 years	34016	99.4	0.6	0.01	<0.0001	23767	99.9	0.1	0.004	<0.0001
30-39 years	44848	96.4	3.5	0.1		30419	99.3	0.6	0.03	
40-49 years	53032	87.3	12.4	0.2		33189	97.4	2.5	0.1	
50-59 years	37587	71.4	27.8	0.8		20921	88.5	11.3	0.2	
60-69 years	8087	56.1	42.6	1.3		4487	76.8	22.6	0.6	
Social class I	7024	86.3	13.4	0.3	<0.0001	6497	96.2	3.7	0.1	<0.0001
Social class II	25007	85.9	13.9	0.3		28247	96	3.9	0.1	
Social class III	145539	87.4	12.2	0.3		78039	95.9	4	0.1	
Non-smokers	115886	85.3	14.4	0.3	<0.0001	79796	95.5	4.4	0.1	<0.0001
Smokers	61684	90.7	9	0.3		32987	97	2.9	0.1	
Underweight	2063	96.5	3.4	0.1	<0.0001	3959	97.7	2.3	0	<0.0001
Normal weight	67771	92.8	6.9	0.2		58138	96.9	3	0.1	
Overweight	71842	85.7	14.1	0.3		30942	95.0	4.9	0.1	
Obesity	35894	78.8	20.5	0.6		19744	94.3	5.5	0.1	
Total	177570	87.2	12.5	0.3		112783	96.0	3.9	0.1	

FIB-4 FIBROSIS estimated with 4 simple elements.

Table 4: Multinomial logistic regression

	FIB-4 intermediate-high		FIB-4 high	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Female	1		1	
Male	3.52 (3.40-3.64)	<0.0001	3.30 (2.66-4.09)	<0.0001
18-29 years	1		1	
30-39 years	2.04 (1.95-2.12)	<0.0001	1.76 (1.44-2.15)	<0.0001
40-49 years	6.00 (5.74-6.28)	<0.0001	5.86 (4.64-7.41)	<0.0001
50-59 years	22.21 (20.90-23.60)	<0.0001	20.55 (14.24-29.65)	<0.0001
60-69 years	124.37 (108-79-142.18)	<0.0001	95.6 (42.07-217.23)	<0.0001
Social class I	1		1	
Social class II	1.25 (1.21-1.30)	<0.0001	1.27 (1.21-1.34)	<0.0001
Social class III	1.48 (1.40-1.56)	<0.0001	1.57 (1.48-1.67)	<0.0001
Non-smokers	1		1	
Smokers	1.36 (1.32-1.40)	<0.0001	1.40 (1.29-1.51)	<0.0001
Underweight	1		1	
Normal weight	1.42 (1.37-1.46)	<0.0001	1.55 (1.28-1.88)	<0.0001
Overweight	1.63 (1.38-1.93)	<0.0001	1.78 (1.49-2.13)	<0.0001
Obesity	1.88 (1.81-1.95)	<0.0001	1.84 (0.68-4.97)	<0.0001

FIB-4 FIBROSIS estimated with 4 simple elements. OR Odss ratio.

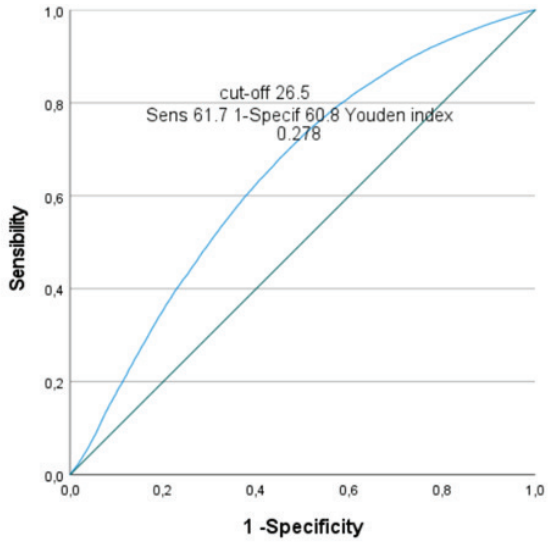

Figure 2: ROC curve FIB-4 high according BMI

Discussion

The fibrosis-4 index (FIB-4) is a widely used tool for the non-invasive assessment of hepatic fibrosis, particularly in patients with chronic liver diseases such as viral hepatitis and non-alcoholic fatty liver disease (NAFLD). This marker has proven effective in stratifying the risk of advanced fibrosis based on easily obtainable clinical parameters, such as age, transaminases (AST and ALT), and platelet count (18). However, demographic and lifestyle factors such as age, gender, social class, smoking, and body mass index (BMI) can significantly influence FIB-4 values, which warrants a thorough discussion due to their impact on the accuracy of diagnosing and managing hepatic fibrosis.

Age is a key factor in interpreting FIB-4 values as it is directly incorporated into the calculation formula. Our results align with studies showing that FIB-4 values tend to increase with age, even in individuals without significant chronic liver diseases, which could lead to an overestimation of fibrosis severity in older patients (19). This is because platelet counts tend to decrease and transaminases may slightly increase with age, factors that affect the FIB-4 formula (20). A recent study suggests that FIB-4 cutoffs should be adjusted according to age, with higher limits for patients over 65 years old to avoid misdiagnosing advanced fibrosis in this population (21). Despite these considerations, age remains an important factor that not only reflects the accumulation of liver damage over time but also the physiological aging process that can influence liver markers.

Gender has also been shown to impact FIB-4 values, although the underlying mechanisms are not fully understood. Various studies have observed that women tend to have lower FIB-4 values compared to men, findings that are consistent with our results. This could be related to differences in transaminase levels and hepatic regenerative capacity, which may be more robust in women (22). Additionally, men tend to develop cirrhosis and hepatocellular carcinoma at a higher rate than women, suggesting that hormonal factors may play a role in the progression of hepatic fibrosis (23). However, differences in body composition and the metabolism of alcohol and fats between genders could also influence the interpretation of FIB-4, highlighting the need to adjust cutoff points based on gender in future studies.

Social class, often represented by socioeconomic status, has an indirect but important influence on the development and progression of hepatic fibrosis. Patients from lower social classes often have limited access to preventive medical care and adequate therapies, which contributes to delayed diagnosis of hepatic fibrosis and, in many cases, a higher prevalence of risk factors such as alcohol consumption, obesity, and exposure to hepatotoxins (24). Several studies have shown a correlation between low socioeconomic status and a higher prevalence of chronic liver diseases such as NAFLD and viral hepatitis, which in turn raises FIB-4 values (25). On the other hand, those from higher social classes tend to benefit from better living conditions, including a healthier diet and lower consumption of harmful substances, which may result in lower FIB-4 values and slower progression of hepatic fibrosis (26). Our study also found that lower social status increased FIB-4 values.

Smoking is another risk factor associated with the progression of hepatic fibrosis and an increase in FIB-4 values in our study. Smoking generates oxidative stress and promotes systemic inflammation, both of which are implicated in liver damage and fibrosis (27). A recent study demonstrated that chronic smokers have significantly higher FIB-4 values compared to non-smokers, even after adjusting for other liver-related risk factors (28). Although the exact mechanism through which smoking promotes hepatic fibrosis is not fully elucidated, it has been postulated that smoking exacerbates hepatocellular injury and reduces the liver's regenerative capacity, leading to increased fibrosis (29). Additionally, smoking is associated with other risk factors such as alcoholism, which can exacerbate liver damage and complicate the interpretation of FIB-4.

BMI is a critical factor in the interpretation of FIB-4 values, particularly in the context of NAFLD. Obesity is one of the main contributors to fat accumulation in the liver, which can progress to non-alcoholic steatohepatitis (NASH) and hepatic fibrosis (30). Studies have shown that patients with elevated BMI tend to have higher FIB-4 values due to the greater likelihood of developing NASH and fibrosis (31). However, the use of FIB-4 in obese patients may be limited, as systemic inflammation and metabolic changes associated with obesity can influence the biochemical markers included in the FIB-4 calculation, potentially leading to an overestimation of fibrosis severity (8). Therefore, in patients with elevated BMI, it is essential to complement FIB-4 with other diagnostic methods, such as elastography or liver biopsy, for a more accurate assessment of fibrosis.

One of the key strengths of the study is its large sample size, which includes more than 340,000 workers, as well as the wide range of variables analyzed.

However, there are also some limitations. Liver fibrosis was not measured using direct methods, but rather through an indirect, validated scale, as the size of the sample made direct measurement impractical. Another limitation is that the study was conducted on a working population aged 18 to 69, meaning the findings cannot be generalized to the broader population.

Conclusions

In summary, age, gender, social class, smoking, and BMI are important factors that influence FIB-4 values and the progression of hepatic fibrosis. Age and gender should be taken into account when interpreting FIB-4 results, especially in older populations or those with marked gender differences. Social class and smoking are modifiable risk factors that can negatively impact the progression of hepatic fibrosis, highlighting the importance of prevention and early treatment. Finally, elevated BMI is strongly associated with NAFLD and fibrosis, requiring a more integrated diagnostic approach. As new tools are developed and cutoffs are adjusted, it is essential to consider these factors to improve the diagnostic accuracy of FIB-4 in hepatic fibrosis.

Conflict of interest: The authors report no conflict of interest.

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Ethical approval: The study adhered to the 2013 Helsinki Declaration and all relevant ethical standards for research. Participants' privacy and anonymity were rigorously protected throughout the process. The study received approval from the Balearic Islands Research Ethics Committee (CEI-IB), with reference number IB 483/20. All data collected were anonymized, with only the principal investigator having access to participants' identities. In accordance with Organic Law 3/2018, passed on December 5, 2018, participants retained the right to access, correct, delete, or oppose the processing of their personal data. This legislation also provides for the protection of digital rights.

Informed consent: Written informed consent was obtained from all individual participants and/or their gaurdians.

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Data availability: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Contributions

Research concept and design: MTGG, AALG, MPL, MJR, HE, RBL

Data analysis and interpretation: MTGG, AALG, MPL, MJR, HE, RBL

Collection and/or assembly of data: MTGG, AALG, MPL, MJR, HE, RBL

Writing the article: MTGG, AALG, MPL, MJR, HE, RBL

Critical revision of the article: MTGG, AALG, MPL, MJR, HE, RBL

Final approval of the article: MTGG, AALG, MPL, MJR, HE, RBL

All authors read and approved the final version of the manuscript.

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