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ORIGINAL

Association between nonalcoholic fatty liver disease risk scales and metabolic syndrome scales in 418.343 spanish workers

Asociación entre las escalas de riesgo de enfermedad de hígado graso no alcohólico y las escalas de síndrome metabólico en 418.343 trabajadores españoles

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Abstract

Introduction: Non-alcoholic fatty liver disease (NAFLD) and metabolic syndrome (MetS) are two very frequent cardiometabolic disorders that seem to be related. The aim of this study is to search for this relationship.
Material and methods: Descriptive and cross-sectional study in 418343 Spanish workers in which the relationship between six NASH risk scales and three of MS was assessed.
Results: The mean values and the prevalence of elevated values of the NASH risk scales are higher in people with metabolic syndrome with the different criteria. In the multivariate analysis we observed that the risk of presenting metabolic syndrome with the three criteria is greater the higher the value of the different non-alcoholic fatty liver disease risk scales. The analysis of the ROC curves shows that the areas under the curve are, in general, very high, with the highest values corresponding to the metabolic syndrome when the IDF criteria are applied with all the NAFLD risk scales.
Conclusions: In our study the different NASH risk scales are quite useful in predicting the occurrence of metabolic syndrome, especially when using the IDF criteria.

Key words: non-alcoholic fatty liver disease, metabolic syndrome, fatty liver.

Resumen

Introducción: La enfermedad del hígado graso no alcohólico (EHGNA) y el síndrome metabólico (SM) son dos alteraciones cardiometabólicas muy frecuentes que parecen estar relacionadas. El objetivo de este trabajo es buscar esa relación.
Material y métodos: Estudio descriptivo y transversal en 418343 trabajadores españoles en los que se valora la relación entre seis escalas de riesgo de EHGNA y tres de SM.
Resultados: Los valores medios y la prevalencia de valores elevados de las escalas de riesgo de EHGNA son mayores en las personas que presentan síndrome metabólico con los diferentes criterios. En el análisis multivariante observamos que el riesgo de presentar síndrome metabólico con los tres criterios es mayor cuanto mayor es el valor de las diferentes escalas de riesgo de hígado graso no alcohólico. El análisis de las curvas ROC muestra que las áreas debajo de la curva son, en general, muy elevadas correspondiendo los valores más altos al síndrome metabólico cuando se aplican los criterios IDF con todas las escalas de riesgo de EHGNA.
Conclusiones: En nuestro estudio las diferentes escalas de riesgo de EHGNA son bastante útiles para predecir la aparición de síndrome metabólico, especialmente cuando empleamos los criterios IDF.

Palabras clave: enfermedad del hígado graso no alcohólico, síndrome metabólico, hígado graso.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is currently the most prevalent liver disorder in the world, affecting one in four people[1] and continues to increase at a worrying rate[2] and is the main cause of liver-related morbidity and mortality[3]. NASH has been related to different pathological entities such as obesity[4], type 25 diabetes, dyslipidemia[6], arterial hypertension[7] and insulin resistance[8]. In the initial stages, triglyceride accumulation is observed in hepatocytes, which increases as new elements of the metabolic syndrome appear[9]. This initial phase, called isolated hepatic steatosis, is a benign process, although a percentage of them will develop significant inflammatory activity that will progress to nonalcoholic steatohepatitis, with or without fibrosis[10].

Metabolic syndrome is a pathological entity that groups together physiological, analytical and clinical alterations that will increase the risk of presenting cardiometabolic alterations that could lead to death. In summary, insulin resistance, excess abdominal fat, atherogenic dyslipidemia, endothelial dysfunction and elevated blood pressure, among others, usually coexist in this clinical picture[11].

The aim of this study is to assess the relationship between NAFLD and metabolic syndrome as determined with different scales.

Material and methods

Descriptive and cross-sectional study carried out in 418.343 workers from different Spanish regions and belonging to different labor sectors, mainly public administration, health, construction and commerce. The workers included in this research were selected from the health examinations performed between the months of January 2017 and December 2019 in the different companies participating in the study. The inclusion criteria were as follows: age between 18 and 69 years, working in one of the companies included in the study, not being on temporary disability, signing the informed consent to participate in the study and to use their data for epidemiological purposes.

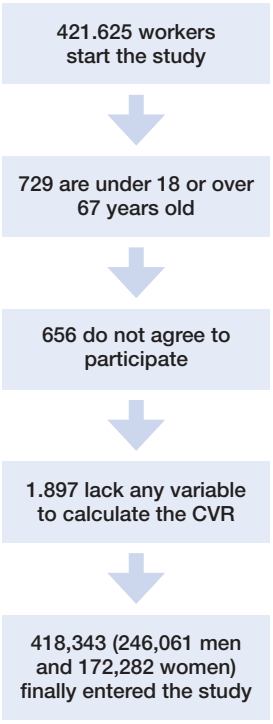
Figure 1 shows the flow diagram of the study participants.

Measurements and data collection

Different anthropometric and analytical parameters were determined in all the participants in the study.

The anthropometric (height and weight), clinical and analytical measurements were performed by health professionals from the different companies participating in the study, after standardization of the measurement techniques.

Figure 1: Flow chart.



To determine weight (in kg) and height (in cm), a SECA 700 scale with an attached SECA 220 telescopic measuring rod was used. Waist circumference (WC) was measured with a SECA measuring tape while the person was standing upright, with feet together, trunk straight and abdomen relaxed. The tape was placed parallel to the floor at the level of the last floating rib.

Blood pressure was obtained with a calibrated OMRON M3 automatic sphygmomanometer and with the person seated and after a 10-minute rest. Three measurements were taken at one-minute intervals and the mean of the three was obtained. The determinations of the different parameters in blood were obtained after 12 h of fasting. The samples were sent to reference laboratories and processed within 2-3 days. Automated enzymatic methods were used to determine glucose, total cholesterol and triglycerides. HDL-c was determined by a precipitation process with dextran sulfate-MgCl2. LDL-c was calculated using the Friedewald formula (valid for triglyceride values below 400 mg/dL). The values of all these parameters are expressed in mg/dL.

Friedewald formula:
LDL = colesterol – HDL – tryglicerides/5

To assess the metabolic syndrome (MS) we used 3 different criteria, the National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP-III), the Joint Interim Statement (JIS) and the update of the International Diabetes Federation (IDF)[12].

The risk of NAFLD is determined by applying different scales:

- Fatty liver index[13]

$FLI = (e^{0.953*\log_e (triglycerides) + 0.139*BMI + 0.718*\log_e (GGT) + 0.053*waist\ circumference - 15.745}) / (1 + e^{0.953*\log_e (triglycerides) + 0.139*BMI + 0.718*\log_e (GGT) + 0.053*waist\ circumference - 15.745}) \times 100$

FLI values are considered to be high risk if they are above 60.

- Hepatic steatosis index (HSI)[14]

HSI= 8 × AST/ALT + BMI + 2 if diabetes + 2 if female
Values are considered to be high risk if they are above 36.

- Zhejian University index (ZJU index)[15]

ZJU= BMI + glycaemia (mmol L) + tryglicerides (mmol L) + 3 AST/ALT + 2 if female
Values are considered to be high risk if they are above 38.

- Fatty liver disease index (FLD)[16]

FLD = BMI + tryglicerides + 3 × (AST/ALT) + 2 × hyperglicaemia (present = 1; absent = 0).
Values are considered to be high risk if they are above 37.

- Framingham steatosis index (FSI)[17]

FSI = –7.981 + 0.011 × age (years) – 0.146 × sex (woman= 1; man = 0) + 0.173 × BMI (kg/m^2) + 0.007 × tryglicerides (mg/dL) + 0.593 × hypertension (yes = 1; no = 0) + 0.789 × diabetes (yes = 1; no = 0) + 1.1 × AST/ALT ratio ≥ 1.33 (yes= 1; no = 0)

- Lipid accumulation product (LAP)[18]

Men (waist (cm) – 65) × (tryglicerides (mMol))
Women (waist (cm) – 58) × (tryglicerides (mMol))

Values are considered to be high risk if they are above 42,7.

Smoker is any person who has smoked at least one cigarette/day (or its equivalent in other types of consumption) in the last month, or who has stopped smoking less than a year ago.

Social class was determined by applying the proposal of the social determinants group of the Spanish Society of Epidemiology[19]. Three categories were considered:

Class I: directors/managers, university professionals, sportsmen and artists;
Class II: intermediate occupations and skilled self-employed workers;
Class III: unskilled workers.

Statistical analysis

A descriptive analysis of the categorical variables was performed, calculating the frequency and distribution of the responses for each of them. For quantitative variables, the mean and standard deviation were calculated following a normal distribution.

Bivariate association analysis was performed using the chi2 test (with correction for Fisher's exact statistic when conditions required it) and Student's t test for independent samples (for comparison of means). Multivariate techniques were used to establish the variables associated with the most significant risk factors. For multivariate analysis, logistic regression was used, with calculation of the odds ratio and the Hosmer-Lemeshow goodness-of-fit test. ROC curves were performed, and the area under the curve

(The statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) version 28.0 (IBM Company, New York, NY, USA) for Windows, with an accepted statistical significance level of 0.05.

Ethical considerations and/or aspects

The research team undertook at all times to follow the ethical principles of health sciences research established nationally and internationally (Declaration of Helsinki), paying special attention to the anonymity of the participants and the confidentiality of the data collected. Approval was requested from the Ethics and Research Committee of the Balearic Islands (CEI-IB), which was obtained with indicator IB 4383/20. Participation in the study was voluntary, so the participants gave their written and oral consent to participate in the study after receiving sufficient information about the nature of the study. To this end, they were given an informed consent form, as well as an information sheet explaining the objective of the study.

The data collected for the study were identified by a code and only the person responsible for the study can relate these data to the participants. The identity of the participants will not be disclosed in any report of this study. The investigators will not disseminate any information that could identify them. In any case, the research team undertakes to strictly comply with the Organic Law 3/2018, of December 5, on the protection of personal data and guarantee of digital rights, guaranteeing the participant in this study that he/she may exercise his/her rights of access, rectification, cancellation and opposition of the data collected.

Results

Table I shows the anthropometric and clinical characteristics of the individuals included in the study. A total of 418343 (246061 men and 172282 women) were included in the analyses. The mean age of the sample was 40.2 ± 11.0 years with the largest group being between 30 and 49 years. Anthropometric, clinical and analytical values were higher in men. Most of the

workers, 75.9% were of social class III. One out of three workers were smokers.

Mean values of the different nonalcoholic fatty liver disease risk scales according to the presence or absence of metabolic syndrome with the three criteria by sex.

Table II shows the mean values of the different nonalcoholic fatty liver disease risk scales according to the presence or absence of metabolic syndrome with the three criteria in men and women. The mean values of all the aforementioned risk scales show much higher values, in both sexes, in persons with metabolic syndrome with the three criteria.

Table III shows the results of the multivariate analysis using multinomial logistic regression. The risk of presenting metabolic syndrome with the three criteria is greater the higher the value of the different non-alcoholic fatty liver disease risk scales.

Figure 2 and **table IV** show the ROC curves of the different NASH risk scales for predicting the presence of metabolic syndrome applying the three criteria in both sexes. It can be seen that the areas under the curve are, in general, very high, with the highest values corresponding to the metabolic syndrome when the IDF criteria are applied with all the NASH risk scales.

Table V shows the cut-off points, sensitivity, specificity and Youden index of the different NASH risk scales for predicting the presence of metabolic syndrome with the three criteria. We observe that the highest levels of sensitivity, specificity and Youden index also correspond to the different EHGNA scales for predicting metabolic syndrome with the IDF criteria.

Table I: Characteristics of the population.

	Women n=172.282 Mean (SD)	Men n=246.061 Mean (SD)	Total n=418.343 Mean (SD)	p-value
Age	39.6 (10.8)	40.6 (11.1)	40.2 (11.0)	<0.0001
Height	161.8 (6.5)	174.6 (7.0)	169.4 (9.3)	<0.0001
Weight	66.2 (14.0)	81.4 (14.7)	75.1 (16.2)	<0.0001
BMI	25.3 (5.2)	26.7 (4.5)	26.1 (4.8)	<0.0001
Waist	74.8 (10.6)	86.2 (11.1)	81.5 (12.2)	<0.0001
SBP	117.4 (15.7)	128.2 (15.5)	123.7 (16.5)	<0.0001
DBP	72.6 (10.4)	77.8 (11.0)	75.6 (11.0)	<0.0001
Cholesterol	190.6 (35.8)	192.6 (38.9)	191.8 (37.7)	<0.0001
HDL-c	56.8 (8.7)	50.3 (8.5)	53.0 (9.1)	<0.0001
LDL-c	116.1 (34.8)	118.0 (36.7)	117.2 (35.9)	<0.0001
Triglycerides	89.1 (46.2)	123.7 (86.4)	109.5 (74.6)	<0.0001
Glycaemia	87.8 (15.1)	93.3 (21.3)	91.0 (19.2)	<0.0001
	%	%	%	p-value
18-29 years	20.7	18.8	19.6	<0.0001
30-39 years	29.7	27.6	28.4	
40-49 years	29.6	30.0	29.9	
50-59 years	16.8	19.7	18.5	
≥60 years	3.2	3.9	3.6	
Social class I	6.9	4.9	5.7	<0.0001
Social class II	23.4	14.9	18.4	
Social class III	69.7	80.3	75.9	
Non smokers	67.2	66.6	66.9	<0.0001
Smokers	32.8	33.4	33.2	

BMI Body mass index. SBP Systolic blood pressure. DBP Diastolic blood pressure. HDL-c High density lipoprotein-cholesterol. LDL-c Low density lipoprotein-cholesterol

Table II:

Men	Non MS ATPIII Mean (SD) n=204597	Yes MS ATPIII Mean (SD) n=41464	p-value	Non MS IDF Mean (SD) n=213558	Yes MS IDF Mean (SD) n=32503	p-value	Non MS JIS Mean (SD) n=178147	Yes MS JIS Mean (SD) n=67914	p-value
FLI	30.9 (23.1)	70.8 (22.5)	<0.0001	31.5 (23.1)	79.2 (15.6)	<0.0001	27.0 (20.5)	65.1 (23.9)	<0.0001
HSI	35.7 (6.1)	42.4 (7.1)	<0.0001	35.6 (6.0)	44.2 (6.7)	<0.0001	35.1 (5.8)	41.6 (7.0)	<0.0001
ZJU	35.9 (4.7)	43.4 (6.0)	<0.0001	35.9 (4,7)	44.8 (5.5)	<0.0001	35.3 (4.4)	42.4 (5.7)	<0.0001
FLD	31.0 (4.6)	37.6 (5.7)	<0.0001	30.9 (4.5)	39.1 (5.1)	<0.0001	30.4 (4.3)	36.7 (5.4)	<0.0001
FSI	0.2 (0.1)	0.4 (0.2)	<0.0001	0.2 (0.1)	0.5 (0.2)	<0.0001	0.1 (0.1)	0.4 (0.2)	<0.0001
LAP	24.2 (20.8)	69.2 (52.2)	<0.0001	24.7 (21.3)	78.4 (53.3)	<0.0001	21.3 (17.1)	59.2 (46.6)	<0.0001
Women	**n=155772**	**n=16510**	**p-value**	**n=156169**	**n=16113**	**p-value**	**n=153102**	**n=19180**	**p-value**
FLI	14.0 (16.5)	56.3 (26.6)	<0.0001	13.8 (16.2)	60.0 (23.2)	<0.0001	13.6 (16.3)	53.5 (25.9)	<0.0001
HSI	35.4 (6.2)	44.9 (7.1)	<0.0001	35.3 (6.1)	45.7 (6.7)	<0.0001	35.3 (6.2)	44.2 (7.0)	<0.0001
ZJU	35.9 (5.3)	46.0 (6.4)	<0.0001	35.9 (5.2)	46.5 (5.8)	<0.0001	35.8 (5.3)	45.2 (6.2)	<0.0001
FLD	29.2 (5.1)	38.4 (6.2)	<0.0001	29.1 (5.1)	39.0 (5.5)	<0.0001	29.1 (5.1)	37.7 (5.9)	<0.0001
FSI	0.1 (0.1)	0.4 (0.2)	<0.0001	0.1 (0.1)	0.4 (0.2)	<0.0001	0.1 (0.1)	0.4 (0.2)	<0.0001
LAP	14.9 (12.4)	48.0 (32.4)	<0.0001	14.7 (12.2)	50.6 (31.0)	<0.0001	14.6 (12.1)	45.9 (31.0)	<0.0001

FLI Fatty liver index. HSI Hepatic steatosis index. ZJU Zhejiang University index. FLD Fatty liver disease. FSI Framingham Steatosis index. LAP Lipid accumulation product. MS ATPIII. Metabolic syndrome Adult Treatment Panel III. MS IDF Metabolic syndrome International Diabetes Federation. Metabolic syndrome Joint Interim Statement.

Table III: Multinomial logistic regression.

	MS NCEP ATP III OR (CI 95%)	p-value	MS IDF OR (CI 95%)	p-value	MS JIS OR (CI 95%)	p-value
FLI low	1	<0.0001	1	<0.0001	1	<0.0001
FLI moderate	2.29 (2.15-2.45)		2.79 (2.60-2.99)		2.93 (2.76-3.11)	
FLI high	6.18 (5.56-6.86)		7.44 (6.53-8.49)		9.55 (8.76-10.41)	
HSI low	1	<0.0001	1	<0.0001	1	<0.0001
HSI moderate	1.19 (1.11-1.27)		1.72 (1.51-1.96)		1.12 (1.05-1.19)	
HSI high	1.63 (1.34-1.98)		21.24 (10.47-43.07)		1.64 (1.40-1.92)	
ZJU normal	1	<0.0001	1	<0.0001	1	<0.0001
ZJU high	2.99 (2.70-3.31)		3.28 (2.88-3.72)		2.45 (2.26-2.66)	
FLD normal	1	<0.0001	1	<0.0001	1	<0.001
FLD high	1.32 (1.28-1.36)		1.45 (1.41-1.48)		1.11 (1.05-1.16)	
LAP normal	1	<0.0001	1	<0.0001	1	<0.0001
LAP high	2.82 (2.60-3.06)		4.30 (3.88-4.77)		2.54 (2.39-2.71)	

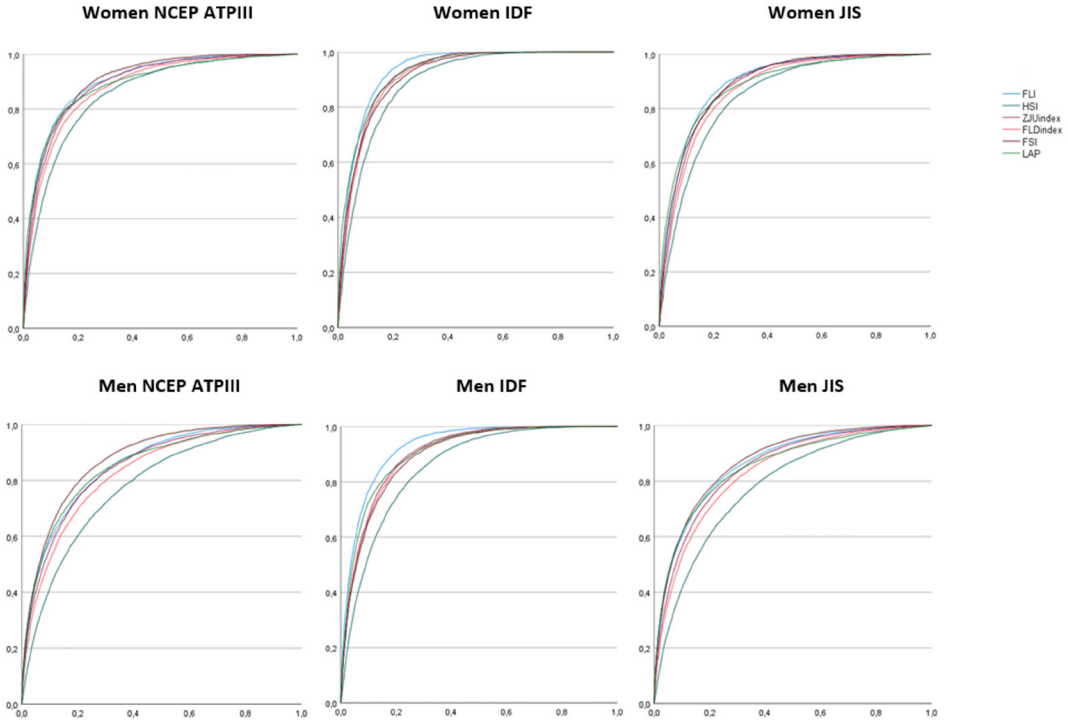
FLI Fatty liver index. HSI Hepatic steatosis index. ZJU Zhejiang University index. FLD Fatty liver disease. LAP Lipid accumulation product.
MS ATPIII. Metabolic syndrome Adult Treatment Panel III. MS IDF Metabolic syndrome International Diabetes Federation. Metabolic syndrome Joint Interim Statement

Table IV: Areas under the curve of the different nonalcoholic fatty liver disease risk scales for predicting the presence of metabolic syndrome with the three criteria by sex.

	Women n=172.282		
	MS NCEP ATPIII AUC (95% CI)	**MS IDF AUC (95% CI)**	**MS JIS AUC (95% CI)**
Fatty liver index	0.900 (0.895-0.906)	0.935 (0.931-0.938)	0.897 (0.892-0.902)
Hepatic steatosis index	0.855 (0.848-0.862)	0.891 (0.886-0.896)	0.849 (0.843-0.855)
Zhejian University index	0.892 (0.887-0.898)	0.921 (0.918-0.925)	0.887 (0.882-0.892)
Fatty liver disease index	0.879 (0.873-0.885)	0.916 (0.912-0.920)	0.874 (0.869-0.880)
Framingham steatosis index	0.904 (0.899-0.909)	0.916 (0.911-0.920)	0.895 (0.890-0.900)
Lipid accumulation product	0.890 (0.884-0.897)	0.928 (0.925-0.932)	0.888 (0.883-0.894)
	Men n=246.061		
Fatty liver index	0.856 (0.851-0.860)	0.928 (0.926-0.931)	0.863 (0.859-0.866)
Hepatic steatosis index	0.779 (0.774-0.785)	0.855 (0.851-0.860)	0.781 (0.776-0.786)
Zhejian University index	0.848 (0.843-0.853)	0.905 (0.901-0.908)	0.850 (0.845-0.854)
Fatty liver disease index	0.829 (0.823-0.834)	0.900 (0.896-0.904)	0.832 (0.828-0.837)
Framingham steatosis index	0.877 (0.873-0.881)	0.895 (0.891-0.899)	0.871 (0.868-0.875)
Lipid accumulation product	0.851 (0.846-0.856)	0.908 (0.904-0.912)	0.852 (0.847-0.856)

MS ATPIII. Metabolic syndrome Adult Treatment Panel III. MS IDF Metabolic syndrome International Diabetes Federation. Metabolic syndrome Joint Interim Statement

Figure 2: ROC curves with the three criteria by sex.



MS ATPIII. Metabolic syndrome Adult Treatment Panel III. MS IDF Metabolic syndrome International Diabetes Federation. Metabolic syndrome Joint Interim Statement

Table V: Cut-off points, sensitivity, specificity and Youden index of the different nonalcoholic fatty liver disease risk scales for predicting the presence of metabolic syndrome with the three criteria by sex.

	Women n=172.282		
	MS NCEP ATPIII Cutoff-Sens-Specif-Youden	MS IDF Cutoff-Sens-Specif-Youden	MS JIS Cutoff-Sens-Specif-Youden
Fatty liver index	27.08-82.7-82.7-0.654	31.10-86.3-86.2-0.725	25.20-82.5-82.4-0.649
Hepatic steatosis index	39.40-78.3-78.2-0.565	40.00-81.5-81.4-0.629	39.09-77.8-77.8-0.556
Zhejian University index	40.30-81.7-81.7-0.634	41.00-85.0-85.0-0.700	39.90-81.2-81.1-0.623
Fatty liver disease index	33.06-80.4-80.4-0.608	33.82-84.3-84.1-0.684	32.74-80.0-80.0-0.600
Framingham steatosis index	0.18-82.0-82.0-0.640	0.19-83.5-83.5-0.670	0.18-80.2-80.0-0.602
Lipid accumulation product	25.60-82.0-82-0.640	27.30-85.0-85.0-0.700	24.44-81.3-81.3-0.626
	Men n=246.062		
Fatty liver index	52.21-77.3-77.0-0.543	61.14-85.2-85.2-0.704	47.11-78.4-78.3-0.567
Hepatic steatosis index	38.22-71.0-71.0-0.420	39.25-77.6-77.4-0.550	37.54-71.2-71.2-0.424
Zhejian University index	39.00-77.0-76.9-0.539	39.94-82.5-82.5-0.650	38.22-77.1-77.1-0.542
Fatty liver disease index	33.65-75.2-75.2-0.505	34.64-82.0-81.9-0.639	32.96-75.6-75.5-0.511
Framingham steatosis index	0.23-79.6-79.5-0.591	0.25-81.5-81.5-0.630	0.20-78.7-78.7-0.574
Lipid accumulation product	37.54-77.8-77.8-0.556	41.86-83.2-82.9-0.661	33.55-77.8-77.7-0.555

MS ATPIII. Metabolic syndrome Adult Treatment Panel III. MS IDF Metabolic syndrome International Diabetes Federation. Metabolic syndrome Joint Interim Statement

Discussion

In our group, the values of the different NASH scales show higher mean values in persons with metabolic syndrome with the three criteria used. The analysis of the ROC curves allows us to affirm that all the NASH risk scales are quite useful for predicting the appearance of metabolic syndrome, although the greatest areas under the curve, sensitivity, specificity and Youden index are found when applying the IDF criteria.

We have not found articles that assess the relationship between NASH and MS risk scales, so we will focus our discussion on assessing whether or not there is a relationship between the two entities.

An article in Lancet20 in 2014 entitled "Non-alcoholic fatty liver disease as a cause and a consequence of metabolic syndrome" already showed a relationship between both clinical entities by observing that two key elements of metabolic syndrome such as glycemia and tryglicerides were underproduced by the liver, so that it can be considered a key element in these metabolic alterations. Another link between the two entities is that both obesity and excessive consumption of sugars or a sedentary lifestyle increase the prevalence of both. Another 2015 study21 that also assessed the relationship between the two pathological conditions concluded that NASH is not simply the hepatic manifestation of metabolic syndrome, but is a pathogenic determinant of the syndrome. Subsequent research22 has emphasized the relationship between NAFLD and MS, indicating that since NAFLD is generally associated with insulin resistance, abdominal obesity, dyslipidemia, hypertension, and hyperglycemia, NAFLD is often considered the hepatic manifestation of the metabolic syndrome. There is evidence that this relationship between NAFLD and metabolic syndrome is bidirectional, as NAFLD may predispose to metabolic syndrome, which in turn may increase NAFLD or increase the risk of its development in those without a prior diagnosis.

Strengths and limitations

As strengths of the study, we can highlight the large sample size (more than 400,000 workers) and the large number of NASH and metabolic syndrome risk scales used. The main limitation is that no diagnostic techniques for NASH or other than risk scales were used.

Conclusions

According to the results obtained in our study, we can conclude that in this group of workers the different NASH risk scales are quite useful for predicting the appearance of metabolic syndrome, especially when we use the IDF criteria.

Conflict of Interest

The authors declare that no competing interests exist.

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