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Prevalence of Nonalcoholic Fatty Liver Disease in a Spanish Town: A Population-Based Study

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Keywords:

Prevalence; Nonalcoholic fatty liver disease (NAFLD); Metabolic associated fatty liver disease (MAFLD); Non-alcoholic steatohepatitis; Fatty liver

Abbreviations:

AST: Aspartate transaminase; ALT: Alanine transaminase; GGT: Gamma-glutamyl transpeptidase; AF: Alkaline phosphatase; A1AT: Alpha 1 antitrypsin; SMA: Anti-smooth muscle antibodies

1. Abstract

1.1. Objective: Nonalcoholic Fatty Liver Disease (NAFLD) is the most important cause of hepatic steatosis and hypertransaminasemia in western countries. The objective was to evaluate the prevalence of NAFLD among a population of 261025 people in the East Valladolid public healthcare area in Spain.

1.2. Methods: We randomly selected 1800 participants from a public healthcare system card database, representing over 95% of the population. We performed a medical history, including measuring anthropometric parameters, abdominal ultrasound, and blood tests to rule out hepatic disease in all patients. We calculated the FLI score in all patients.

1.3. Results: 448 participants agreed to participate in the study. Prevalence of nonalcoholic fatty liver disease in our study was 25.45% [21.4%-29.5%]. Prevalence was highest between 50 and 70 years, increasing with age ($p<0.006$). There were no significant differences in sex ($p=0.073$). The median Body mass index was 27.2, and NAFLD was related to the weight ($p<0.001$) and abdominal perimeter ($p<0.001$). Logistic regression analysis showed GGT lower than 26 UI/ml, steatosis in ultrasound, and HOMA IR greater than 2.54 as independent factors to predict NAFLD in the liver disease subpopulation. NAFLD diagnosis matched with an elevated FLI score in 87.3% of cases.

1.4. Conclusion: The prevalence of NAFLD is very high, according to other epidemiological studies. A complete study with a clinical consultation, image studies, and blood test in all patients allow assessing the prevalence of NAFLD in the population reliably.

2. Main Text

2.1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is the leading cause of hypertransaminasemia in western countries [1-3]. NAFLD includes a broad disease spectrum from simple steatosis to fatty cirrhosis [4-7]. Disease progression may lead to nonalcoholic steatohepatitis (NASH) or even advanced cirrhosis in some patients [5-9]. NAFLD is, in fact, the first cause of cryptogenic cirrhosis in the population [5, 10, 11], and this is the reason why it is so important to diagnose it in the early stages and make a correct follow up.

Liver biopsy is the only proven way to perform NAFLD diagnosis accurately. This method is not recommended in all patients due to its aggressive nature and the excellent prognosis of most NAFLD pa-

tients. Alternatives for diagnosis may be imaging techniques such as ultrasound, computerized tomography o magnetic resonance combined with a blood test to identify other causes of liver disease. Ultrasound elastography in the liver is a novel method to stratify severity according to liver stiffness, and it also allows the evaluation of the steatosis degree using a CAP probe (Controlled attenuation parameter) (43). Several studies validated this method for NAFLD [14].

Several studies have evaluated the prevalence of NAFLD or NASH by using different methods [1, 2, 15-21]. Only a few of them use diagnostic procedures that are accurate enough to diagnose NAFLD or NASH reliably. Many studies use patients admitted to the hospital or patients on an outpatient basis. Thus their results could not be extrapolated to the population (Table 1).

We performed a prospective, cross-sectional study in 1800 randomly selected people groups to evaluate NAFLD prevalence in Spain. Our objective was also to detect factors associated with NAFLD risk.

Table 1: Main prevalence studies in nonalcoholic fatty liver disease

Study	Year	N	Source population	Ultrasound	ALT, ASP, and GGT (alcohol and virus excluded)	Biopsy	Estimated prevalence
Nomura (38)	1986	4613	Factory workers (men)	Yes (CT in obese)	Yes (alcohol evaluated but virus not excluded)	No	Hypertransaminasemia in nonobese nondrinkers 24% Steatosis obese nondrinkers 47%
Hultcrantz (41)	1986	149	hypertransaminasemia	Yes	Yes	No	NAFLD 36.7%
Nomura (43)	1988	2574	General population	Yes	No	No	NAFLD 14%
Wanless y Lentz (25)	1990	351	Inhospital autopsy	No	No	Yes	18.5% (NASH obese) 2.8% (NASH non obese)
El-Hassan (32)	1992	1243	Clinic patients	Yes (CT)	No	No	NAFLD 9.7%
Lonardo (42)	1997	363	General population	Yes	No	No	NAFLD 19.8%
Parés (33)	2000	1801	Factory workers (men)	Yes	Yes (alcohol not excluded)	No	Steatosis 13.8%
Bernal-Reyes (44)	2000	92	Healthy volunteers	No	No	Yes	NASH 10.3% Diabetic (18.5%) Non diabetic (7.1%)
Dyonisos Study (36)	1993 Publ. 2001	6917	General population	Yes (sick patients)	Yes	No	Steatosis 58% of Hypertransaminasemia patients (GOT or GPT 13.1%)
Del Gaudio (40)	2002	216	Vertical gastroplasty surgery	No	Yes (alcohol and virus excluded)	Yes	NAFLD 77.8% NASH 6%
Omagari (45)	2002	3432	Inhospital patients (retrospective)	Yes	Yes (virus not excluded)	No	NAFLD 9.3%
NHANES III	2003	15676	General population	No	Yes	No	Hypertransaminasemia 7.9%
Beymer (23)	2003	48	Gastric bypass surgery (morbid obesity)	No	No	Yes	NAFLD 85% NASH 33%
Browning (18)	2004	2287	General population	NMR	Yes (virus not excluded, alcohol excluded)	No	Steatosis 37%
Shalhub (46)	2004	154	Bariatric surgery (bypass)	No	Yes (virus not excluded)	Yes	NAFLD 79% NASH 35%
Ground (39)	2005	423	Plane traffic accident victims	No	No	Yes	NAFLD 15.6% NASH 2.5%
Szczepaniak (34)	2005	2349	Pop. Dallas Heart Study (18-65a)	Yes spectrometry MNR	No (alcohol evaluated)	No	Steatosis 33.4% (nondrinkers)
Pendino GM (2)	2005	1605	General population	Yes (sick patients)	Yes	No	NAFLD 24% in patients with hypertransaminasemia. 3% of general population
Jimba S (28)	2005	1955	Health surveys	Yes	Yes (not fasting insulin)	No	NAFLD 29%
Park SH (27)	2006	6648	Health survey	Yes	No (virus excluded,lípids, Clinical history)	No	NAFLD 18.7%
Zelber-Sagi (47)	2006	352	General population	Yes	Yes	No	NAFLD 30%
Papatheodoritis (24)	2007	3063	Blood donors	No	Yes	No	15% (NASH)
Chen CH (1)	2007	3260	General population	Yes	Yes (not fasting insulin but ALT))	No	NAFLD 21.2%
Caballería L (16)	2010	766	General population	Yes	Yes	No	NAFLD 25.8%
Williams CD (48)	2011	400	Retired and inactive military	Yes	No	Yes	NAFLD 46%

2.2. Methods

The target population was people from the age of 18 without any other restriction. Alcohol consumption was not an exclusion criterion.

We randomly selected one thousand eight hundred people from a Public healthcare database. This database includes 99% of the population in Spain (social security). We calculated the population size to reach an alfa error of 4% with a 95% confidence and an estimated prevalence of 20%.

The estimated participation was 20-25%. Our reference population was people from Valladolid, a middle size town (521661 people) in Castilla y León region, Spain. We obtained the sample from people in the East Valladolid health area (279723 people). East Valladolid Primary Care Management provided data with adequate permission. We also got Local Research commission permission.

We made the randomization according to the health care point size. Therefore the number of participants coming from every health care point in the sample was proportional to its population.

Participants were recruited sequentially by health care points. Recruitment methods were telephone calls and ordinary mail. The first method was mailing, and if more than 20% of people in one healthcare point were not recruited, we contacted them by phone.

We obtained informed consent from every participant, and the study protocol adjusted to the ethical guidelines of the 1975 declaration of Helsinki. All participants underwent a medical record, a blood test, and abdominal ultrasonography. The medical record included familial and personal background, alcohol consumption, smoking habit, diabetes, hypertension, bariatric surgery, recent parenteral nutrition, physical activity, and hepatotoxic drug intake.

We measured all patients' height, weight, and abdominal perimeter (at the hip and waist).

Blood tests included AST, ALT, AP, total bilirubin and fractions, fasting glucose, total cholesterol, triglycerides, hemoglobin, mean corpuscular volume, creatinine, homocysteine, and total protein. Two expert radiologists made the ultrasonography using a 3.5 MHz convex probe. Some participants were assessed simultaneously by the two radiologists to homogenize criteria, but we did not calculate the Kappa index. Ultrasonography evaluated steatosis, space-occupying lesions, and cirrhosis signs.

We considered liver disease patients when they fulfilled at least one criterion in blood tests or ultrasound (see Table 2). Analytic criteria included AST>38, ALT>41, and GGT>50. Ultrasound criteria were steatosis (any degree), cirrhosis, or echogenicity disorders.

We repeated blood tests and clinical consultations in patients with liver disease to determine the etiology. This second medical record emphasized alcohol consumption, the familial background of hepatic disease, and underlying factors for steatosis. Table 3 summarizes specific blood tests performed. We calculated the FLI score (fatty liver index score) in the liver disease patients without liver steatosis to evaluate NAFLD's probability in this subgroup. We also calculated the NFS (NAFLD fibrosis score) in all patients.

We consider hypertransaminasemia if AST > 38 UI/l, ALT> 41 UI/l, or GGT > 50 UI/l. We diagnosed NAFLD in patients with hypertransaminasemia or steatosis without significant alcohol intake or other liver diseases (see Table 3). We excluded patients with daily alcohol consumption higher than 30 grams (alcoholic liver disease). We suspected hemochromatosis when the transferrin saturation index was higher than 45%, ferritin higher than 350 ng/ml, and hypertransaminasemia. We considered autoimmune hepatitis if hypertransaminasemia, hepatic autoantibodies, and hypergammaglobulinemia (see Table 3). Once diagnosed, we analyzed the FLI score and the NFS in NAFLD patients.

Table 2: Disease definition in the screening phase of the study

Disease definition	
Ultrasound criteria	Blood test criteria
Any steatosis degree	AST > 38 UI/ml
Echogenicity disorders suggesting chronic hepatopathy	ALT > 41 UI/ml
Cirrhosis	GGT > 50 UI/ml
Hepatic SOL suggesting malignancy	Alkaline Phosphatase >129 UI/l†

† Alkaline Phosphatase elevation due to bone metabolism or other extrahepatic causes must be previously ruled out. SOL: Space occupying lesions

Table 3: Laboratory test in the protocol to study liver disease

Laboratory test			
Glucose metabolism	**Hepatic profile**	**Ferric metabolism**	**Serology, hormones, hemogram, coagulation**
Fasting glucose	AST	Transferrin	Platelet count
Fasting insulin	ALT	Transf. saturation index	Hemoglobin (g/dl)
HbA1C	GGT	Ferritin	Serology vs. C, B, and A Hepatitis virus
HOMA index	AST/ALT index	Sideremia	Serology HIV
C Peptide	Albumin		INR, TTPA, Fibrinogen
	Total protein		TSH, T4
	Amylase	**Proteinogram**	Urinary ethanol
	Alkaline phosphatase		
	Bilirubin and fractions	**Specific liver diseases screening**	**Autoimmune hepatitis antibodies:**
			Antinuclear antibodies, Anti DNA
		Ceruloplasmin	LKM,anti-smooth muscle, LC-1,
		Alpha 1 antitrypsin	SLA, SLP, antimitochondrial
		Cooper levels in the blood.	

Glycosylated Hemoglobin

2.3. Statistical Analysis

We showed variables with average and 95% confidence intervals. We assessed normal distribution using the Kolmogorov Smirnov test for every variable. We used the T student test to compare continuous and dichotomous variables when they followed a normal distribution. If we did not achieve the normal distribution, we performed a Mann-Whitney test. We completed the ANOVA test to compare continuous variables with qualitative variables with three or more categories following a normal distribution. If they didn't, we performed a Kruskal Wallis test. The Chi-Square test compared dichotomous variables following a normal distribution and Fisher exact test if they didn't.

We used the stepwise logistic regression analysis to perform the multivariate analysis. Multivariate analysis was only applied to the liver

disease group, as we performed some blood tests only in this group. The dependent variable was the dichotomous variable presence or absence of nonalcoholic fatty liver disease. We selected those variables statically significant in the univariate analysis for the multivariate analysis. Then we transformed continuous variables in dichotomous using a cutoff point. These cutoff points are determined clinically if the variable has an established cutoff point or using COR curves if not. We performed statistical analysis using SPSS 18.0 software.

3. RESULTS

3.1. NAFLD Prevalence

Four hundred forty-eight people agreed to participate in our study (from 1800 people. We mostly recruited 425 patients (95%) by mail and 23 by phone (5%). We obtained informed consent from every participant.

We summarized the Baseline characteristics of our participants in table 4. According to official data, median age, sex, and urban/rural distribution were comparable to the population. We performed the recruitment, data collection, and follow-up between December 2008 and April 2009.

Median age was 53.44 [51.9-54.9] years (range from 23 to 90). 49.7% [47.3% - 52.08%] were male and 51.3% female. 24.3%0 [20.33%-28.2%] of participants had hypertension and 8.4% [5.83%-10.96%] diabetes. 29.2% [24.9%-33.4%] of participants were smokers (media 12.41 [10.8-13.9] cigarettes/day). Median alcohol consumption was 10.14 [8.27-12.01] grams a day. 0.9% (2) of women drank more than 30 g a day, whereas 19.97% (44) of men did with a statistically significant difference (p<0.0001).

170 participants (37.94% [33.4%-43.4%]) were classified as patients with liver disease according to our experimental procedure. 78 patients (45.88% [41.2%-50.4%]) presented hypertransaminasemia. 127 patients (74.7% [70.6%-78.7%]) had ultrasonographic disorders, and. 35 patients more had both hypertransaminasemia and ultrasonographic disorders (37.95% [33.45%-42.44%]).

Of 170 patients with hepatic disease, 114 fulfilled NAFLD criteria (Figure 1). The prevalence of NAFLD was 25.45% [21.4%-29.5%] in the population. We also found 28 patients with alcoholic liver disease (6.25% [4.01%-8.49%]), 15 patients with drug-induced hepatopathy (2.46% [1.02%-3.89%]), two patients with B hepatitis, five patients with C hepatitis, two more with suspected hemochromatosis, two with suspected bacterial overgrowth, and two with suspected autoimmune hepatitis (all 6 suspected cases were later confirmed in regular consultations)

We based NAFLD diagnosis in steatosis (ruled out alcohol and drugs) in 100 patients. We diagnosed with NAFLD based on hypertransaminasemia (ruled out other causes of liver disease) in 14 patients. 29 patients diagnosed with NAFLD had both steatosis and hypertransaminasemia.

The median FLI score was 64.04 in patients classified as NAFLD and 36.9 in the other participants (p<0.001). In the NAFLD group, FLI score was higher than 60 points (fatty liver high risk) in 69/111 patients (62.2%), intermediate-risk (30 to 60 points) in 29/111 (26.1%), and low risk (lower than 30 points) in 13/111 (11.7%).

NAFLD fibrosis score (NFS) in our NAFLD cohort showed a low risk of fibrosis (estimated fibrosis F0-F2, NFS lower than -1.455) in 67/111 (60.4%). Intermediate-risk fibrosis was present in 40/111 (36%), with an NFS from -1.455 to 0.675. We found High-risk fibrosis (estimated fibrosis F3-F4) with NFS higher than 0.675 in 4/111 patients (3.6%).

NAFLD appears in all ages. Most cases match the 50 to 70 years' group, with 46.7% (52) of patients in this range (Figure 2). There were no significant differences in sex (p=0.073) with 65 men and 49 women. We didn't find any difference in body mass index between men and women (p=0.205).

The distribution of NAFLD was similar in urban and rural areas (p=0.103), and we found no difference in weight in both groups (p=0.289).

Table 4: Baseline characteristics

		Average in the population	Average and confidence interval in liver disease	p-valuee
Weight (in Kilograms)	*Global*	73.16	78 [75,98-80,02]	p=0,0001
	Men	80,12	82,5 [80,11-85,05]	
	Women	66,24	71,2 [68,45-74,01]	
Body Mass Index	*Global*	27,2	29 [28,36-29,65]	p=0,0001
	Men	27,4	28,56 [27,78-29,33]	
	Women	26,9	29,73 [28,6-30,86]	
Systolic blood pressure		130.44	135,5 [132,94-138,22]	p=0,0001
Waist perimeter		93,4	99,14 [97,46-100,81]	p=0,0001
Hip perimeter		95,9	99,37 [97,93-100,8]	p=0,0001
Waist to Hip ratio	*Men*	65% >1	72,55% >1	p=0,0001

	Women	94,2% <1	74,6% <1	
Prior illness				
Hypertension		24.30%	35% [27,82-42,17]	p=0,0001
Type 2 diabetes		8,40%	15% [9,63-20,36]	p=0,0001
Consumption habits				
Alcohol	*Global*	10,14	14,93 [10,95-18,91]	p=0,011
	Men	17,8	23,38 [17,32-29,44]	
	Women	2.5	2,25 [0,88-3,62]	
Tobacco	*N° Cigarettes*	12,41	3,24 [2,15-4,32]	p=0,138
	Men	30.5%(68)	2,15 [0,94-3,36]	
	Women	28%(63)	3,98 [2,36-5,60]	
	% Smokers	29,20%	24,71% [18,22-31,19]]	

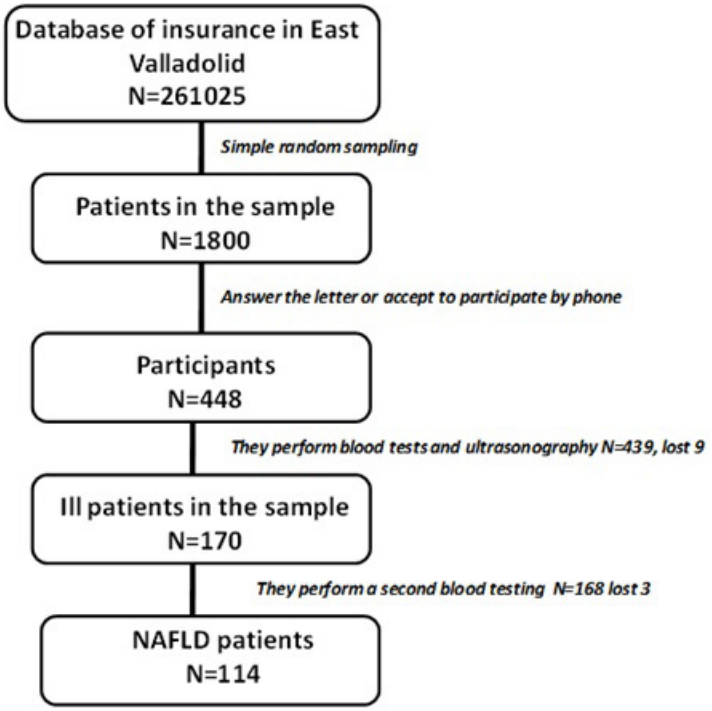

Figure 1: The flow chart in the study

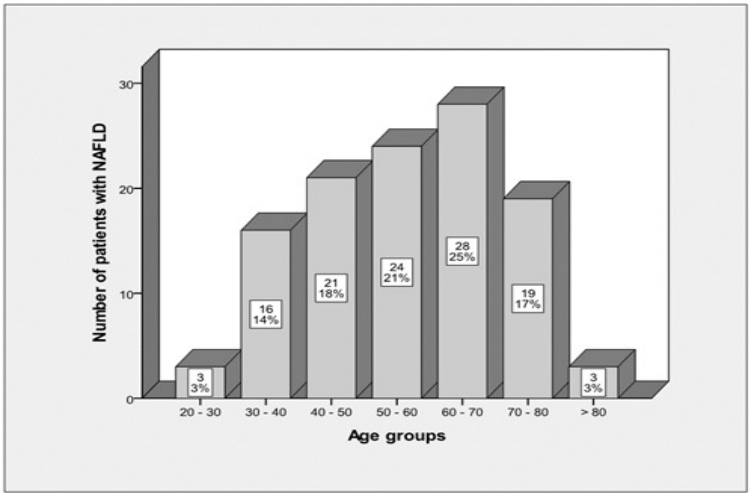

Figure 2: NAFLD prevalence according to age

3.2. Factors related to NAFLD

We found statistical differences of NAFLD prevalence in patients with type 2 diabetes (p<0.0001). NAFLD was present in 52.6% [36.7%-68.5%] of the type 2 diabetes group versus 22.9% [18.8%-46&26.9%] of non-diabetic patients. NAFLD was also more frequent in patients with hypertension (p<0.0001). While NAFLD was present in 38.5% [29.3%-47.6%] of patients with hypertension, it was diagnosed in 21.2% [16.8%-25.5%] of non-hypertensive patients. Systolic blood pressure was 6.9 [3.1-10.7] mm of Hg higher in patients with NAFLD (p<0.0001) compared with controls, and diastolic blood pressure was 3.2 [1.3-5.1] mm de Hg lower too. Patients with hypertension and type 2 diabetes had NAFLD in 57.7% [38.7%-76.6%], also higher than controls (p<0001).

We did not find any association between NAFLD and sedentarism (p=0.793) or family history of liver disease (p= 0.065).

Patients with NAFLD were 8.2 [5.4-10.9] Kg heavier than healthy people (p<0.001). We found a proportion of obese people of 23.8% [19.8%-27.7%], and the mean body mass index in the population was 27.22[26.83-27.61], so in the overweight range. In our study, the NAFLD proportion was higher as body mass index increased (figure 3), so all patients with morbid obesity had NAFLD.

Umbilical abdominal perimeter (waist perimeter) was 9.6 [7.3-11.8] cm higher in the NAFLD group (p<0.001). A hip perimeter was also associated with NAFLD (p<0.001) in our study. Waist-hip index was higher in the NAFLD group (p<0.001), but it was under 1 (0.99 [0.988-1.011] in NAFLD patients). Obese people subset did not either reach the unit (0.991 [0.978-1.001]) in the waist-hip index.

Fasting glucose was 114.4 [108.5-120.3] mg/dl in the NAFLD group and 100.5 [98.8-102.2] mg/dl in the control group (p<0.0001). Fasting insulin (p=0.002) and HbA1C (p=0.004) were also associated with NAFLD. Insulin resistance was measured by using HOMA (Homeostasis Model Assessment). HOMA-IR (insulin resistance) was associated with NAFLD (p<0.001), being of 3.33 in the NAFLD group and 2.49 in the control group.

HOMA-IR was associated with the steatosis degree (p=0.006), so patients with no steatosis or mild steatosis had a lower HOMA-IR than patients with moderate steatosis (p <0.0001 and p=0.006 respectively). Differences in HOMA-IR between patients with moderate and severe steatosis were not significant (0.937).

Regarding lipid metabolism, triglycerides were associated with NAFLD in the obese patient group (p<0.001) but not in the normal-weight group. There were no significant differences in cholesterol levels in NAFLD patients regarding controls (p=0.167). LDL cholesterol wasn't either also related to NAFLD (0.756).

Alpha 1 antitrypsin was lower in the NAFLD group (p=0.038), being 8.36 [4.6-16.2] mg/dl lower in these patients. We didn't find this association in the rest of the patients with liver disease (p=0.186).

The AST/ALT relation was lower than 1 in the NAFLD group (0.93 [0.75 – 1.11]) compared with 1.11 [1.07-1.16] among the rest of population as classically defined (3) in NAFLD patients.

Cholelithiasis was an associated finding in 12 patients, regarding 2.68% [1.18% - 4.18%] of the population. Cholelithiasis was the most common space-occupying lesion. Cholelithiasis was statically associated with nonalcoholic fatty liver disease (p=0.048), as shown in Figure 4.

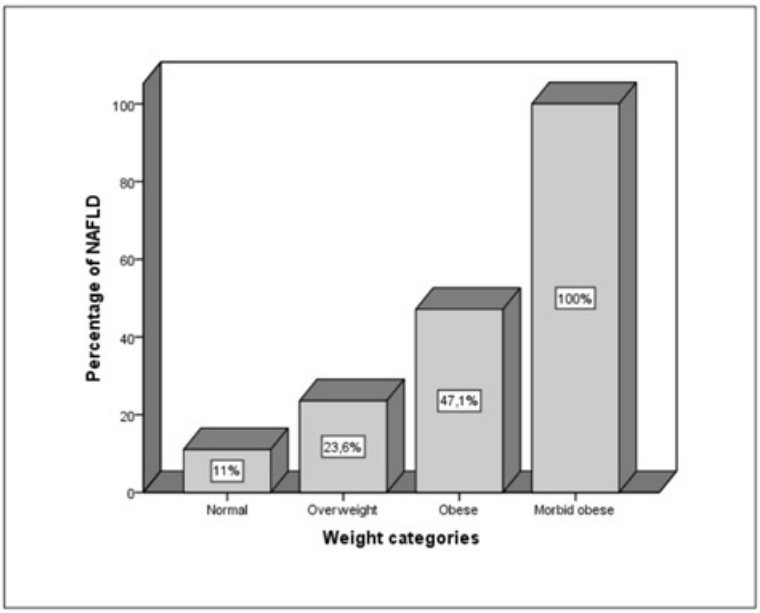

Figure 3: NAFLD prevalence according to weight categories

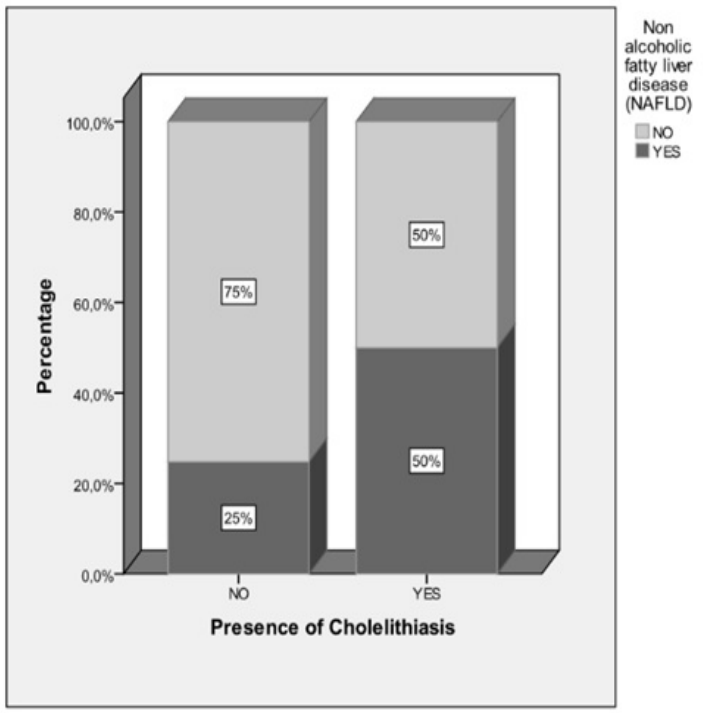

Figure 4: NAFLD proportion in patients with cholelithiasis

3.3. Multivariate Analysis

We included in the multivariate analysis those variables found statically significant in the univariate analysis.

Selected variables were: Age, waist perimeter, waist to hip ratio, weight, type 2 diabetes, hypertension, systolic blood pressure, diastolic blood pressure, glycemia, fasting insulin, glycosylated hemoglobin, HOMA-IR, HOMA 2-IR, HOMA 2% S, Triglycerides, Ferritin, AST, ALT, AST/ALT ratio, GGT, A1AT, ceruloplasmin, urate, number of metabolic syndrome criteria, steatosis degree and lithiasis. Stepwise logistic regression analysis showed GGT lower than 26 UI/ml, steatosis in ultrasound, and HOMA IR greater than 2.54 as independent factors to predict NAFLD in the liver disease subpopulation. This model correctly classified 75% of NAFLD patients. HOMA-IR >2.54 presented an OR 3,668 [1.6-8.3] (p=0.002), GGT<26 presented an OR of 3.18 [1.27-7.95] and presence of steatosis had an OR 5.02 [2.115-11.91]. Even when there was a high relation in univariate analysis, the other variables were covered by the effect of these independent variables. The area under the curve in the COR curve of this logistic regression model to predict NAFLD was 0.775.

4. Discussion

We randomly selected the sample participants from a public healthcare system database. This database includes 99.3% of the population in Castilla y León (and its capital Valladolid). All healthcare points were included in our health area, so participants are representative of the whole community. We avoided selection bias this way.

24.88% of 1800 people accepted to participate (448 participants). These data match those reported in other studies using mail as a recruiting method [22]. We cannot exclude non-response bias since non-responders could have a different epidemiologic profile (healthier people a priori) compared with participants. We partially controlled the non-responder bias by using non-responders substitution. This way, if the responder's rate was lower than 20% in one health center, additional recruitment methods were used. The primary alternative method was phoning participants alphabetically from the database until the response rate reached 25%. We only recruited a few patients following this method.

Alcohol consumption was higher in men, and excessive consumption (more than 30 grams daily) was also higher (10.26%). Tobacco consumption was over one-third (29.2% [24.9%-33.4%]), with similar data to the Spanish Health Minister of 29.5 %.

The experimental procedure allows us to rule out most hepatic diseases, which is one of the study's main strengths compared to other similar studies performed before.

The NAFLD prevalence found in our study of 25.45% [21.4%-29.5%] was similar to that found in other studies using different methods. Those only based on image tests such as ultrasonography or Magnetic resonance show prevalence rates between 9.7% and 19.8% [17, 23-26]. Those based on blood tests showed lower prevalence rates (7.9-15% of the population) [27, 28]. Biopsy-based studies demonstrated different prevalence according to the reference population. Those performed in bariatric surgery patients had a higher NAFLD prevalence (71-85%).

Four studies combine imaging techniques and blood tests [2, 9, 21, 29, 30]. This way, the diagnosis might be more accurate as diagnostic procedures are similar to those used in clinical practice. Two of these studies (Zelber- Sagi et al. [21] and Caballería et al. [9] are remarkable because they study healthy volunteers a priori and rule out most hepatic liver diseases. NAFLD prevalence results were also similar to our study (30 and 25.8%, respectively).

We found lower levels of alpha one antitrypsin in NAFLD patients (8.36 [4.6-16.2] mg/dl inferior in the NAFLD group). These finding has not been reported in NAFLD patients before. A1AT is an essential enzyme in innate immunity, and enzymatic deficiency leads to a pro-inflammatory state. Heterozygosity for A1AT mutations contributes to liver damage and influences inflammation and iron metabolism (50). We must confirm this finding in biopsy studies.

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