



Prognostic value of non-alcoholic fatty liver disease in the elderly patients

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Abstract

Background Non-alcoholic fatty liver disease (NAFLD) is the liver manifestation of metabolic syndrome, a risk factor for mortality and cardiovascular morbidity, but we ignore the role of steatosis per se in survival, and there is very little information about this condition in the geriatric patient.

Aims With the present study, we investigated the independent prognostic value of NAFLD on overall mortality in the elderly.

Methods Within the Pianoro Project, involving people ≥ 65 years, anamnestic, clinical and laboratoristic data related to NAFLD, insulin resistance, diabetes/hyperglycemia, hypertension, obesity and dyslipidemia were collected in 804 subjects (403 male, 401 female). These subjects were followed up for mortality for a median time of 12.6 years. A multivariate analysis was performed to evaluate the prognostic value of the covariates.

Results At Kaplan–Meier estimator the presence of NAFLD seems to be associated to a lower mortality, and survival tends to increase with the increasing of steatosis grade. Cox's analysis found that survival is increased for subjects having hypercholesterolemia (RR = 0.565), NAFLD (RR = 0.777), hypertension (RR = 0.711) and in female (RR = 0.741), while it is decreased for the older subjects (RR = 3.046), in patients with hypertriglyceridemia (RR = 1.699) and for diabetics (RR = 1.797). The variables BMI and HDL-cholesterol have no role.

Conclusion The data obtained in our study show that NAFLD is not associated to overall mortality in the elderly population.

Keywords Non-alcoholic fatty liver disease · Elderly · Metabolic syndrome · Diabetes

Introduction

Non-alcoholic fatty liver disease (NAFLD) is characterized by excessive hepatic fat accumulation, associated with insulin resistance. NAFLD includes two distinct conditions: non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH), with an increased risk of fibrosis progression, cirrhosis and possibly hepatic comorbidities such as hepatocellular carcinoma (HCC) [1, 2]. NAFLD is the most common liver disorder in Western countries, affecting 17–46% of adults [3, 4] and in these countries NAFLD has reached epidemic proportions [5, 6]. There is a strong correlation between NAFLD and metabolic syndrome (MS).

NAFLD might represent an additional characteristic, or the hepatic manifestation, of MS [7, 8].

Some studies have recently evaluated NAFLD in the elderly population. An association between sarcopenia in the elderly and hepatic steatosis has been documented. There is an inverse correlation between insulin resistance and muscle mass, and a direct association between insulin resistance and steatosis [9, 10]. A potential common mechanism between sarcopenia and NAFLD is the chronic low-grade inflammation that characterizes aging, commonly called "inflammaging" [11, 12].

Some studies showed that NAFLD might represent a risk factor for the development of dementia. This association could be linked to the increased cerebrovascular risk (increased incidence of atherosclerotic carotid plaques in subjects with NAFLD), but hormonal factors may also play a role [13–15].

The aim of the present study was to evaluate the epidemiological features of NAFLD in the elderly population and its relationship with MS. We also evaluated, in this age group,

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the independent prognostic relevance of NAFLD on overall mortality, to consider the opportunity to treat this common condition in geriatric patients, which have peculiarities in terms of limitation in physical activity, higher risk of drug interactions and adverse reactions.

Materials and methods

Study setting and study design

Our study is part of a larger cross-sectional and prospective study about the promotion of physical activity in the elderly population called “The Pianoro Study”.

The study started in November 2003 and recruited 3255 subjects, aged over 65 years, of both sexes, resident in Pianoro, who received a postal questionnaire to evaluate: the presence of risk factors for atherosclerosis, their quality of life, the previous or actual cardiovascular diseases, their degree of autonomy, prescribed medications and the amount of physical activity performed in the last week. There were no exclusion criteria apart from age.

Two thousand twenty-three subjects (62% of the population) filled in the questionnaire and sent it back by ordinary mail. All the subjects over 65 resident in Pianoro, whether they had answered the questionnaire, were invited to their general practitioner’s office, where gave written informed consent to take part in the study, had a check of the previously filled questionnaire, received a paperpencil cognitive test (Mini Mental State Examination) and a weight, height and blood pressure evaluation.

Between January 2004 and January 2005 they were also invited to come to our hospital division, where we collected anthropometric parameters, fasting blood samples, an electrocardiogram, an abdominal ultrasound scan and a sub-maximal step test.

In all, 1144 subjects, 550 men and 594 women, aged 65–91 years (median 71), performed all clinical steps of the study without missing data.

Fourteen years after the study start (between December 2016 and March 2018), we tried to evaluate the outcome of these subjects (death or survival) deducing information from their accesses to the National Health Service. In this way, we found data of 804 of them.

Variables examined

Age, gender and anthropometry

Age, gender, weight, height and waist circumference (measured in centimeters with the patient standing at the umbilicus level) were assessed. BMI was calculated as the ratio between weight (kg) and the square of height (m). According

to the BMI [16] we classified the population in class 0 (BMI < 25 kg/m²), class 1 (BMI 25–29.9 kg/m²), class 2 (BMI 30–35 kg/m²) and class 3 (BMI > 35 kg/m²). Class 0 corresponds to normal weight or underweight; class 1 corresponds to overweight, class 2 or 3 to obesity.

Four skinfolds were measured: biceps skinfold, triceps skinfold, subscapular skinfold and suprailiac skinfold.

According to the age, the population of our study was divided into two subgroups: between 65 to 74 years old (young old) and over 74 years old (old old and oldest old, not further subdivided due to the small number of people over 85 years).

Laboratory assays

Blood glucose, creatinine, total cholesterol, HDL-cholesterol and triglycerides were assayed with enzymatic methods. Also insulin was measured with an analytical sensitivity of 0.2 mU/l.

Lifestyle, diseases and multimorbidity

Variables evaluated were:

- Alcohol intake: defined as the daily use of at least one alcoholic unit (a glass of wine or a pint of beer or a small glass of spirit).
- Diabetes: subjects with a history of diabetes according to the American Diabetes Association Criteria, and/or on anti-diabetes drugs and/or with blood glucose > 126 mg/dl were considered diabetic.
- Impaired fasting glucose (IFG): subjects with blood glucose > 100 mg/dl but not diabetic.
- Hypertension: subjects with a history of hypertension, those with systolic blood pressure \geq 130 mmHg and/or diastolic blood pressure \geq 85 mmHg and those on current therapy with anti-hypertensive drugs.
- Dyslipidemia: were considered as independent variables hypertriglyceridemia (triglycerides > 150 mg/dl) or current treatment, pathological levels of HDL cholesterol (< 40 mg/dl in men or < 50 mg/dl in women) or current treatment with statins and hypercholesterolemia (total cholesterol \geq 200 mg/dl) or current therapy.
- Insulin resistance: insulin resistance was estimated, according to the homeostasis model assessment (HOMA), with the formula: (fasting insulin [mU/l] \times fasting glucose [mmol/l])/22.5 [17]. In a previous study concerning an Italian population, the cut-off of HOMA values indicative of insulin resistance (above the 75th percentile) was set at 2.7 [18, 19].
- MS: the presence of MS, according to the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III rev. 2004), occurs when at least three of the follow-

ing five criteria are fulfilled: waist circumference > 102 cm in men or > 88 cm in women; blood glucose \geq 100 mg/dl (5.6 mmol/l) or current treatment with hypoglycaemic drugs; triglycerides \geq 150 mg/dl (1.7 mmol/l) or current treatment; HDL cholesterol < 40 mg/dl (1.0 mmol/l) in men or < 50 mg/dl (1.3 mmol/l) in women; systolic blood pressure \geq 130 mmHg and/or diastolic blood pressure \geq 85 mmHg or current treatment with antihypertensive drugs.

- Charlson comorbidity index: multimorbidity was assessed using the Charlson comorbidity index, a scoring system including 19 categories of comorbid conditions and commonly used as prognostic tool for mortality [20].

Abdominal ultrasound scan for evaluating fatty liver, subcutaneous and visceral fat.

The abdominal ultrasound (US) scan was performed using an Esaote-Ansaldo Technos echograph with a 3.5–5 MHz convex US probe. Diagnosis of fatty liver was based on the increased echogenicity of the liver parenchyma. Two physicians with extensive US experience performed each exam. If present, steatosis was classified into three degrees:

- Mild: slightly brighter liver as compared to the renal cortex, clear visualization of diaphragm.
- Moderate: brighter liver with attenuation of the ultrasound beam.
- Severe: very bright liver, severe ultrasound beam attenuation with a marked attenuation of the ultrasound beam, such as not to make visible the portal bifurcation.

With transversal scan in epigastrium/mesogastrium we also evaluated subcutaneous fat (distance between the anterior abdominal wall and the parietal peritoneum) and visceral fat (distance between the anterior abdominal wall and the anterior border of the abdominal aorta, subtracting the subcutaneous fat).

Fat mass percentages

To determine this value it was used the formula of the Siri equation [21]:

$$\%fat = 495/Body\ density - 450$$

Body density was calculated considering the four skinfolds using the formula:

$$Body\ density = 1.1715 - [0.0779 \log_{10} (\text{sum of skinfolds})].$$

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Science (SPSS version 23 for Windows).

Before running the statistical analysis, continuous parametric variables were tested to check the presence of a normal distribution. Descriptive data are presented as mean value \pm standard deviation (SD) or median (range) for continuous variables, and as frequencies and percentages for discrete variables.

The Chi square test (χ^2) was used to evaluate differences between groups in discrete variables. The Mann–Whitney's *U* test was used to compare continuous variables between groups.

To evaluate the prognostic value of NAFLD, Kaplan–Meier survival curves were performed.

We also evaluated prognostic significance, for survival, of other clinical/laboratoristic/anamnestic variables transformed into dichotomic or category parameters, for example presence or absence of diabetes, presence or absence of hypertriglyceridemia etc.

All variables that were significant or nearly significant at univariate time-dependent analysis were considered for multivariate time-dependent analysis according to Cox's Model.

For each variable the adjusted relative risk (RR) and 95% confidence interval (CI) were also computed.

For all tests two-tailed *p* values are reported, and the level of significance was set at *p* < 0.05.

Results

Description of the population

We recruited 804 subjects (403 males and 401 female) in our study. The median age was 72.7 years (65.5–93.6) with 64% of subjects < 75 years (young old) and 36% \geq 75 years.

Their outcomes were evaluated after a median follow-up of 12.6 years (22 days–14 years); 401 of them are still alive, while 403 are dead.

At the end of the follow up the median age was 83.3 years (67.5–99.8 years). Regarding lifestyle, 10% of the population at the time of enrolment was an active smoker, while 48% were ex-smokers; 63% of subjects reported consuming alcoholic beverages, but only 53 subjects (about 6.6% of the population) said they consume more than three alcoholic units for day.

We evaluated our subjects for their comorbidities with the Charlson Comorbidity Index: the median value was 1 (0–10). These data are summarized in Table 1.

Considering the prevalence of the features included in MS definition, according to NCEP-ATP III criteria, we

Table 1 Description of the population of our study

Variables	Values
Subjects enrolled	804
Males:female	403:401
Median age (years)	72.7 (65.5–93.6)
< 75 years (%)	64
≥ 75 years (%)	36
Follow up (years)	12.6 (22 days- 14 years)
Median age at the end of follow up (years)	83.3 (67.5–99.8)
Active smokers (%)	10
Ex-smokers (%)	48
Consume > 3 alcoholic units a day (%)	6.6
Charlson comorbidity index	1 (0–10)

Demographic characteristics, lifestyle, follow up and comorbidity

Prevalence is expressed as a percentage

Descriptive data are presented as median (range)

found that the 44.4%, at first examination, had IFG, while the 12.9% had diabetes; the 70.4% was hypertensive; the 30.3% had hypertriglyceridemia; the 38.1% had low HDL cholesterol; the 52.3% had pathological waist circumference. There are no significant differences in the distribution of these criteria between the two age classes (< and ≥ 75 years).

The prevalence of MS in our population, according to the same criteria, was 44.6%, without significant age-related differences.

Considering our subjects' BMI, we found that the 38.8% was normal or under-weight, the 44.1% over-weight and the 17.1% obese. There is significant difference ($p < 0.001$) between the two age classes in BMI distribution, with a higher prevalence of lower BMI classes in older subjects, likely representative of malnutrition. The average BMI of the whole population is $26.5 \pm 4.0 \text{ kg/m}^2$, while it is $27.1 \pm 4.2 \text{ kg/m}^2$ in the young olds and $25.4 \pm 3.4 \text{ kg/m}^2$ in people over 75.

Additional anthropometric and metabolic features of the enrolled subjects were evaluated. There are significant age-dependent differences in BMI, fat mass percentage, subcutaneous and visceral fat, while there is no difference in the prevalence of insulin-resistance, diabetes and hypercholesterolemia.

All the variables analysed and their differences between the two age classes are reported in Table 2.

Prevalence of hepatic steatosis in the elderly

In our population we found a prevalence of US-diagnosed hepatic steatosis of 42.7%; 26.6% of these subjects had mild steatosis, 13.7% moderate, 2.4% severe. The grade of steatosis tends to decrease moving from the younger age class to the older one with a statistically significant difference (Table 3).

We found a negligible prevalence of drinkers; for this reason, we avoided excluding from our sample this small group

Table 2 Description of the population of our study. Prevalence of pathological conditions and anthropometric evaluation

	All	65–74 years	≥ 75 years	<i>p</i>
IFG (%)	44.4	45.9	41.7	0.254
Hypertension (%)	70.4	70.5	70.3	0.973
Hypertriglyceridemia (%)	30.3	28.9	32.8	0.261
Low HDL-cholesterol (%)	38.1	40.5	33.8	0.06
Pathological waist circumference (%)	52.3	54.5	48.6	0.111
Metabolic syndrome (%)	44.6	44.9	44.1	0.833
Insuline resistance (%)	33.9	35.9	29.9	0.091
Diabetes (%)	12.9	13	12.9	0.931
BMI < 25 (%)	38.8	32.7	49.3	
BMI 25–29.9 (%)	44.1	45.4	41.7	< 0.001*
BMI 30–35 (%)	16.1	20.3	9	
BMI > 35 (%)	1	1.6	0	
Subcutaneous fat (mm)	17 (1–91)	18 (1–60)	16 (1–91)	< 0.001*
Visceral fat (mm)	65 (4–175)	68 (5–175)	61 (4–150)	< 0.001*
Fat mass %	33.9 (± 7.3)	34.5 (± 7.1)	32.6 (± 7.6)	0.003*
Hypercholesterolemia (%)	36.9	37.8	35.4	0.519

Prevalence is reported as percentage. Descriptive data are presented as mean value \pm standard deviation (SD) or median (range)

p differences between 65–74 years and ≥ 75 years

IFG impaired fasting glucose, BMI body mass index

*Significant *p* values

Table 3 General prevalence of steatosis in our population and prevalence of different degrees

Steatosis	All	65–74 years	≥ 75 years	<i>p</i>
Absent (%)	57.3	51.4	67.6	
Present (%)	42.7	48.6	32.4	
Mild steatosis (%)	26.6	26.9	23.4	<0.001*
Moderate steatosis (%)	13.7	18.3	8.3	
Severe steatosis (%)	2.4	3.4	0.7	

Difference of the steatosis between the two age classes
Prevalence is expressed as a percentage. *p* differences between 65–74 years and ≥ 75 years
*Significant *p* values

of subjects (only 53 subjects), and we considered all the individuals with US-diagnosed steatosis as having NAFLD.

Relationship between NAFLD and MS in the elderly

As a first purpose, we evaluated if NAFLD and MS have in the elderly the same tight association as widely confirmed in the adults. We studied if the single features of MS had a different distribution in subjects with and without NAFLD;

Table 4 Prevalence of MS and all its components in subjects with NAFLD and without NAFLD

	without NAFLD	with NAFLD	<i>p</i>
IFG (%)	34.8	57.4	<0.001*
Hypertriglyceridemia (%)	22.2	41.4	<0.001*
Low HDL-cholesterol (%)	32.2	45.9	<0.001*
Hypertension (%)	65.4	77.2	0.001*
Pathological waist circumference (%)	39.4	69.8	<0.001*
Metabolic syndrome (%)	31.5	62.4	<0.001*
Diabetes (%)	8.6	18.6	<0.001*

There is a strong correlation between NADLS and MS
Prevalence is expressed as a percentage
p differences between subjects with NAFLD and without NAFLD
IFG impaired fasting glucose
*Significant *p* values

Table 5 Differences in the distribution of hepatic steatosis between the different BMI classes

Steatosis	BMI < 25 (kg/m ²)	BMI 25–29.9 (kg/m ²)	BMI 30–34.9 (kg/m ²)	BMI > 35 (kg/m ²)	<i>p</i>
Absent (%)	78.8	52.3	22.7	0	<0.001*
Mild steatosis (%)	18.6	29.7	30.5	37.5	<0.001*
Moderate steatosis (%)	2.6	16.9	35.9	50	<0.001*
Severe steatosis (%)	0	1.1	10.9	12.5	<0.001*

Prevalence is expressed as a percentage. *p* differences between prevalence of steatosis between the different BMI classes
*Significant *p* values

all comparisons show wide and statistically significant differences (Table 4).

We also found significant differences in the distribution of hepatic steatosis between the different BMI classes (Table 5).

This data show, in the elderly as in adult subjects, a strong relationship between NAFLD, MS, and associated conditions, such as diabetes and obesity.

Univariate analysis

Survival curves of subjects with hepatic steatosis, diabetes, insulin resistance, hypercholesterolemia, MS and all parameters included in the definition of MS according to the NCEP-ATP III criteria were estimated with Kaplan–Meier analysis. These survival curves were compared with those of subjects not affected by these conditions.

Evaluating the survival curves of subjects with and without hepatic steatosis at the first visit (Fig. 1) we observed that survival is greater in affected subjects, compared to those not affected ($\chi^2 = 5.441$; $p = 0.020$); furthermore, distinguishing survival curves for hepatic steatosis degree, we observed a survival decrease with the reduction of steatosis degree ($\chi^2 = 9.427$; $p = 0.024$), as shown in Fig. 2.

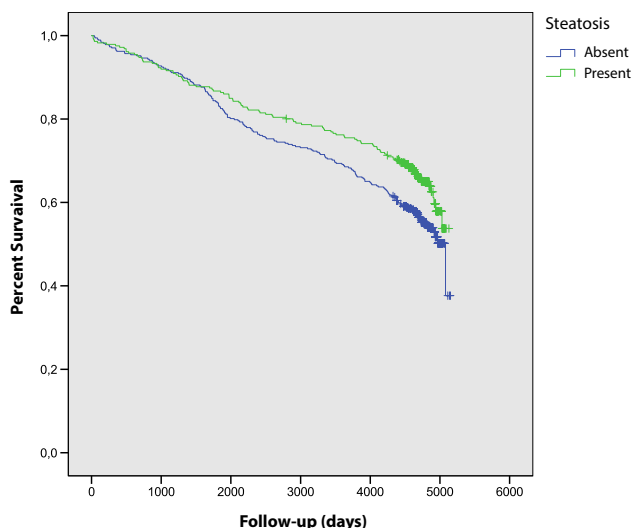


Fig. 1 Survival curves of subjects with and without NAFLD. Survival is greater in subjects with NAFLD

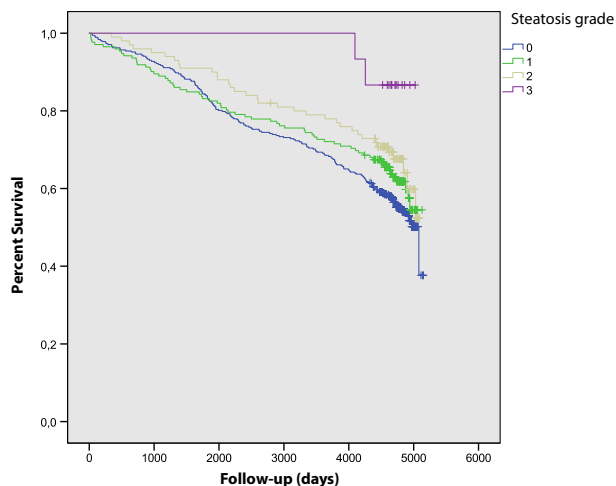


Fig. 2 Survival curves distinguished by degree of hepatic steatosis. There is an higher survival in higher grades of steatosis

At Kaplan–Meier estimate, as expected, survival was increased in younger subjects compared to the older ones ($\chi^2 = 98.739$; $p < 0.001$). Sex is a relevant feature too: survival was increased in females compared to males ($\chi^2 = 5.551$; $p = 0.018$). BMI is not a significant feature ($\chi^2 = 3.270$; $p = 0.071$), although there's a trend to a higher survival for the overweight subjects compared with the subjects under or normal-weight.

We analysed the role of single components of MS on survival. The role of waist circumference is not significant ($\chi^2 = 0.212$; $p = 0.645$), and neither is hyperglycaemia ($\chi^2 = 2.533$; $p = 0.111$); hypertriglyceridemia is associated with a lower survival ($\chi^2 = 6.002$; $p = 0.014$); paradoxically, hypertension ($\chi^2 = 12.959$; $p < 0.001$) and low HDL cholesterol

($\chi^2 = 7.349$; $p = 0.007$) seem to be related to a higher survival. The role of MS itself seems not to be relevant in our population ($\chi^2 = 0.001$; $p = 0.982$).

Survival was decreased for diabetics ($\chi^2 = 9.349$; $p = 0.002$), while hypercholesterolemia is associated to a higher survival ($\chi^2 = 10.862$; $p = 0.001$). Finally the insulin-resistance was evaluated: about survival no difference between people with insulin-resistance and without insulin-resistance was found ($\chi^2 = 0.018$; $p = 0.893$).

The results shown above are summarized in Table 6.

Multivariate analysis

The main aim of our study was the evaluation of NAFLD prognostic significance in old people.

For the purpose to evaluate the independent prognostic value of NAFLD in our population, a backward logistic regression analysis was performed considering in the Cox's model as variables the ones significantly associated to survival at univariate analysis, in a positive or negative way (Table 7).

Cox's analysis result showed that the variables independently associated to survival are:

1. NAFLD: after a median follow up of 12.6 years, the death risk is 22% lower in subjects with NAFLD than without NAFLD;
2. Female sex: the death risk is 26% lower in women than in men;
3. Hypertension: the subjects having a systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg, or being on anti-hypertensive therapy, have a death risk 29% lower than the ones not fulfilling these criteria;
4. Hypercholesterolemia: the death risk is almost halved in hypercholesterolemic subjects.

The variables negatively associated to survival, representing risk factors for overall mortality, apart from obviously age, are:

1. Diabetes: the death risk, after a follow up of 12.6 years, is 80% higher in diabetics;
2. Hypertriglyceridemia: the death risk is 70% higher in subjects having hypertriglyceridemia.

The contribution of the variables BMI and low HDL-cholesterol seems not to be relevant.

Table 6 Variables evaluated on Kaplan–Meier analysis and respective significance in the total population and divided into age classes

	χ^2	<i>p</i> (all subjects)	<i>p</i> (65–74 years)	<i>p</i> (≥ 75 years)
Steatosis	5.441	0.020*	0.241	0.205
Age	98.739	<0.001*	–	–
Female sex	5.551	0.018*	0.008	0.059
Overweight	3.27	0.071	0.704	0.193
Waist circumference	0.212	0.645	0.484	0.234
IFG	2.533	0.111	0.191	0.072
Hypertriglyceridemia	6.002	0.014*	0.182	0.097
Hypertension	12.959	<0.001*	0.003*	0.073
Low HDL-cholesterol	9.349	0.007*	0.013*	0.361
Metabolic syndrome	0.001	0.982	0.903	0.504
Diabetes	9.349	0.002*	0.098	0.002*
Hypercholesterolemia	10.862	0.001*	0.003*	0.011*

Survival curves were compared with survival curves of subjects not affected with the Mantel–Cox or Breslow tests

IFG impaired fasting glucose. χ^2 chi-squared-test. *p* (all subjects), *p* (65–74 years) and *p* (≥ 75 years) differences between our population and control groups

*Significant *p* values

Table 7 Logistic backward regression considering, in the total enrolled population, as variables those significantly associated with survival in the univariate analysis, in a positive or negative way

Variables	χ^2	<i>p</i>	RR	CI 95%
Age class	76.886	<0.001*	3.046	2.375–3.908
Hypercholesterolemia	16.961	<0.001*	0.565	0.430–0.741
Hypertriglyceridemia	14.487	<0.001*	1.699	1.293–2.231
Diabetes	12.369	<0.001*	1.797	1.296–2.492
Hepatic steatosis	8.551	0.003*	0.777	0.656–0.920
Hypertension	6.881	0.009*	0.711	0.522–0.918
Female sex	5.692	0.017*	0.741	0.580–0.948
Excluded variables				
Low HDL-cholesterol	3.406	0.065		
Overweight	0.208	0.648		

The protective role of hypercholesterolemia, hepatic steatosis, hypertension, and female sex is shown. Instead it is reported negative role of the age group, hypertriglyceridemia and diabetes on survival

χ^2 chi-squared-test, *RR* relative risk, *CI* confidence intervals

*Significant *p* values

Discussion

Several studies showed an increased mortality in subjects with NAFLD [22, 23], but studies investigating the independent prognostic value of NAFLD in the elderly population have never been performed.

In our study the median value of Charlson Comorbidity Index was low; it means that, as we expected, our sample is not exactly representative of the whole old population, but it's made of fitter subjects, as the result of a voluntary

enrolment which required a certain degree of autonomy to attend the medical examinations, and so a relatively good health.

This is, in our opinion, not so much a limitation of this study, because it is precisely in this population the doubt arises whether to treat or not to treat NAFLD, and not in multi-pathological or institutionalized subjects.

A relevant information of our study is that MS and all its components, diabetes and insulin-resistance, show high prevalence in old people, with no distribution differences between the two age classes that we considered (< or ≥ 75 years).

On the contrary, according to previous observations, we found significant distribution differences in BMI, fat mass percentage, and subcutaneous and visceral fat: all these variables show higher average values in younger subjects. These differences are an expression of the changes in body composition old people undergo in different phases of aging, differences that have to be considered in therapeutic and nutritional approach to geriatric patient [24].

NAFLD shows a prevalence of 42.7% in the old population recruited in our study, that is definitely higher than reported by other authors for adult subjects [25].

As other metabolic features, according to literature [13], the distribution of NAFLD prevalence in old people show a decreasing trend, with higher average values in younger subjects than in older people.

This trend, similar to the ones of BMI, fat mass percentage, visceral and subcutaneous fat, may suggest that changes in the prevalence of hepatic steatosis in the elderly are part of changes in the body composition, and would not be caused by differences in the prevalence of insulin

resistance and MS, which show a similar distribution in different age groups.

However, this does not stand for a weaker relationship between NAFLD, MS and its single components in the elderly population: this association, according to our results, is important and statistically significant, contrary to other authors' thesis [26].

Other groups [27] suggest that the reducing prevalence of NAFLD in the older people might be an expression of a negative selection of subjects with NAFLD, but this hypothesis seems to be denied by our study, too.

The main purpose of our study was to investigate the independent prognostic value of NAFLD in the elderly. We also evaluated the prognostic significance of all components of the MS. Cox's analysis show that modifiable risk factors for overall mortality in the elderly are diabetes and hypertriglyceridemia, while NAFLD, hypercholesterolemia and elevated blood pressure have no association with overall mortality. Although these results seem to be paradoxical, it must be considered that "traditional" risk factors, in the elderly, often tend to lose their prognostic value, and sometimes to revert it.

With regard to the "hypertension" parameter, probably this paradoxical result is caused, at least in part, to the fact that we considered hypertensive people not only those with high blood pressure but also those in anti-hypertensive therapy (regardless of blood pressure values).

Furthermore, according to recent recommendations on cardiovascular risk in the elderly population [28], the correction of hypertension should not be "aggressive".

The role of hypercholesterolemia should be carefully evaluated in the geriatric patients, too: a slightly increased cholesterolemia may be considered an indirect sign of good nutritional status and has a good prognostic significance in elderly subjects [29]. This data is confirmed by our study, too.

Evaluating the independent prognostic significance of NAFLD our study shows that, in the old population, NAFLD is not associated with an increased overall mortality, differently from studies in adult population suggest.

Some limitations in our study have to be acknowledged: NAFLD was diagnosed just by the US finding of a "bright liver", although its diagnosis would require the exclusion of drinkers and people suffering from other chronic liver diseases. We did not exclude the first ones as subjects exceeding the daily alcohol intake limits were a small group in our population, and there were no significant differences between the ones having NAFLD or not. Instead, we unfortunately did not have information about the prevalence of other chronic liver diseases in our subjects, and we have to underline that HCV infection has a non-negligible prevalence in old population.

Conclusion

The results of our study show, in the old population, no association between NAFLD and overall mortality. On an institutional level, this result can be a cause for reflection in health organizational matter, in particular in terms of allocating resources to treat or to follow up a so common condition in this age class.

Moreover, on a biological level, our data suggest a possible different "biological significance" of NAFLD in the geriatric patients: an indirect marker of good nutritional status.

Anyway, we still must repeat that, in the elderly as in the adult, there is a tight association between NAFLD and MS and, more important than MS in old subjects, a tight association with diabetes. Although NAFLD does not seem to be a risk factor for overall mortality in the elderly, it must be considered an alert for the presence of metabolic comorbidities. These ones, especially diabetes, will possibly deserve a therapy, but not NAFLD per se.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Statement of human and animal rights All procedures and the research protocol have been approved by the locally appointed ethics committee of the University of Bologna. The experimental protocol was designed in accordance with the Declaration of Helsinki (1964).

Informed consent Informed consent was obtained from all individual participants included in the study.

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