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Fatty liver and mortality: a cohort population study in South Italy

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ABSTRACT

Objective Alcoholic fatty liver (AFLD) and non-alcoholic fatty liver (NAFLD) are two common conditions. However, if they can increase the risk of death is poorly explored. We therefore aimed to investigate the potential association between the presence and severity of liver steatosis and mortality in a large sample of older people.

Design Prospective.

Setting Community.

Participants Women and men randomly sampled from the electoral rolls of the population of Castellana Grotte, a town in Southern Italy (Apulia region) between 2005 and 2006. Among 1942 initially contacted, 1708 (=87.9%) participated to the baseline survey (Multicentrica Colelitiasi III (MICOL III)). This specific study included 1445 older participants (mean age=65.2 years, females=44.2%).

Exposure NAFLD or AFLD.

Primary and secondary outcomes Mortality (all-cause and specific-cause).

Results After a median of 12 years, 312 participants (=21.6%) died. After adjusting for nine potential confounders, the presence of steatosis was not associated with any increased risk of death in both NAFLD and AFLD. The severity of liver steatosis was not associated with any increased risk of mortality in NAFLD, while in AFLD, the presence of moderate steatosis significantly increased the risk of overall (HR=2.16; 95% CI 1.19 to 3.91) and cancer-specific (HR=3.54; 95% CI 1.16 to 10.87) death.

Conclusions Liver steatosis is not associated with any increased risk of death in NAFLD, while moderate steatosis could be a risk factor for mortality (particularly due to cancer) in people affected by AFLD.

Strengths and limitations of this study

- The long follow-up (12 years) is a strength of our research.
- The use of liver echography for the diagnosis of liver steatosis (contrary to most studies using biohumoral parameters) is another strength of our work.
- The number of people with severe grade of either AFLD/NALFD is small and this can introduce an important bias in our findings.
- No liver biopsy (the gold standard method for the diagnosis of liver steatosis) is available.
- Comorbidities are self-reported and this could introduce another bias.

INTRODUCTION

Fatty liver seems to be a common condition in Western countries,[1] probably affecting about half of the individuals in some studies.[2] It is estimated that nearly one in every three patients with persistently elevated alanine transaminase might have a fatty liver disease.[3]

Several risk factors have been recognised for the development of fatty liver. Among them, alcohol is probably the most important. Heavy alcohol intake is associated with fatty liver and afterwards with fibrosis, indicating a form called alcoholic fatty liver (AFLD).[4] In Western countries, however, fatty liver is usually associated with abdominal obesity and with metabolic syndrome features[1] underlining a picture called non-alcoholic fatty liver (NAFLD).[1]

Even if the prevalence of the NAFLD varies according to the definition and the country, a recent systematic review and meta-analysis reported an overall prevalence of 25%.[5] Independently from the origin, liver steatosis seems to be a significant predictor of several medical conditions including cardiovascular diseases (CVDs),[6] type 2 diabetes[7] and liver cirrhosis.[1] Metabolic conditions associated with NAFLD included obesity, present in more than half of the people, type 2 diabetes, hyperlipidemia, hypertension and metabolic syndrome.[5] Liver-specific mortality and overall mortality in NAFLD patients is estimated in 0.77 persons per 1000.[5] However, the role of potential confounders seems to be important for explaining the association between the presence of liver steatosis and these medical conditions. For example, the association between liver steatosis and the onset of CVDs disappeared after the adjustment for potential confounders (eg, the

presence of adiposity and diabetes) in some studies.[8] Finally, because NAFLD is a heterogeneous disease, the advanced stages of which seem to be strongly affected by medical conditions (particularly insulin resistance and type 2 diabetes), further modifying the association between liver steatosis and mortality.[9]

Not univocal findings were reported regarding the presence of liver steatosis and mortality. Overall, it seems that a diagnosis of NAFLD is associated with a significant shorter survival than general population mainly due to higher rate of CVD.[10–13] However, other studies reported that NAFLD was not associated with any increased risk of mortality.[14] Moreover, many of the studies investigating the association between liver steatosis and mortality used elevated serum aminotransferases as a marker of NAFLD, which may underestimate the true prevalence of NAFLD of >50%.[11] Finally, very limited data are available regarding the presence and severity of liver steatosis and mortality in people with AFLD.

Given this background, we aimed to investigate the potential association between the presence and severity of liver steatosis, diagnosed through liver echography and mortality in a large sample of older people living in a Mediterranean area.

MATERIALS AND METHODS

Participants

This study included women and men randomly sampled from the electoral rolls of the population of Castellana Grotte, a town in Southern Italy (Apulia region) between 2005 and 2006. Among 1942 initially contacted, 1708 (=87.9%) participated to the baseline survey (Multicentrica Colelitiasi III (MICOL III)). No a priori selection criteria were used for the MICOL III study in terms comorbidities, while only people participating to the first wave in 1985–1986 and coming back 20 years after were included. The participants were enrolled through contact by mail, informing their general practitioners. For this specific research, being mortality the outcome of our interest, a trained researcher manually revised all the death certificates of the participants involved (other details are reported in the Outcome: vital status section).

Written informed consent, given during the first visit, was obtained from each participant before entering the study.

Patient and public involvement

Patients or public were not involved in the conception of the MICOL study.

Measurements

The survey visit consisted of the administration of a standardised questionnaire, including a validated semiquantitative food frequency questionnaire, anthropometric measurements, a blood sample for biochemical tests and an ultrasonographic examination. For the aims of this work, among the data regarding dietary habits, we reported data regarding alcohol intake and daily energy intake. A trained nurse recorded weight, height and waist circumference. The body mass index (BMI) was calculated and reported in kg/m^2. Blood pressure was also recorded measuring one time at the right arm of every participant by a trained nurse. Finally, self-reported information regarding smoking status (active or previous smoking during the first evaluation vs never), the presence of diabetes, gastric ulcer, cholecystic stones, hypertension and acute myocardial infarction, were used in the analyses.

Exposure: fatty liver disease severity

All the subjects underwent a standardised ultrasound examination made by two investigators using a Hitachi H21 Vision (Hitachi Medical Corporation, Tokyo, Japan). People with active chronic hepatitis (eg, HBV or HCV), acute forms, autoimmune hepatitis or haemochromatosis (based on self-reported information) were a priori excluded from this work. Examination of the visible liver parenchyma was performed with a 3.5 MHz transducer. A scoring system was adopted to obtain a semiquantitative evaluation of fat in the liver.[15 16]

The degree of liver fatty infiltration was graded according to the appearance of the liver echotexture, the liver echo penetration and the clarity of the liver blood vessels, as well as the liver diaphragm differentiation in echo amplitude. To each criterion, a score was assigned indicating the level of fatty liver infiltration. For each criterion, a score of 2 indicated a definite positive (++) fatty liver infiltration, a score of 1 a probably positive (+) fatty liver infiltration, a score of 0 the absence of fatty liver presence (–). The fatty liver score ranged from 0 to 6, higher values indicating higher severity. We therefore categorised the severity of liver steatosis in: absent (score=0), mild (score=1 or 2), moderate (score=3 or 4) and severe (score=5 or 6). Liver steatosis was consequently divided in NAFLD or AFLD, using the standard cut-offs for alcoholic liver disease (30 g/day for men and 20 g/day for women).[17] Alcohol intake was determined using the food frequency questionaire (FFQ), as stated before, using the intake of wine, beer and super-alcoholic drinks.

Outcome: vital status

The study's outcome of interest was all-cause mortality. In the MICOL III, mortality was confirmed and adjudicated death certificates manually revised by a trained researcher. The examination of the death certificates was done until 31 December 2017. Cardiovascular death was adjudicated through the codes of the International Classificiation Disease (ICD) 10 from I00 to I99 and cancer-related death with the codes from C00 to C97.

Statistical analysis

The analyses are shown by alcohol intake and by the presence or not of liver steatosis consequently having four groups: NAFLD (ie, liver steatosis with an alcohol intake <30 g/day for men and <20 g/day for women), the

control group of people with NAFLD (ie, no presence of liver steatosis and low alcohol intake), AFLD (liver steatosis and an alcohol intake ≥30 g/day for men and ≥20 g/day for women) and the control group of AFLD (ie, high alcohol intake without any evidence of liver steatosis).

In each group, normal distributions of continuous variables were tested using the Kolmogorov-Smirnov test. Data are shown as mean±SD for quantitative measures, and percentages for all categorical variables. P values were calculated using the independent T-test for continuous variables and χ^2 test for categorical ones.

Incidence rates are reported as number of deaths for 1000 persons-years. The proportional hazards assumption was checked by plotting the Schoenfeld residuals versus time without any violation and then Cox's regression analyses were performed. Using as exposure the presence of liver steatosis (NAFLD or AFLD), the basic model was not adjusted for any confounder; the fully adjusted model adjusted for: age, sex, smoking status (current/previous vs never), presence of diabetes, acute myocardial infarction (all yes vs no); waist circumference, systolic and diastolic blood pressure, daily energy (all as continuous). These covariates used for adjustment were factors significantly different between the presence or not of liver steatosis (considering a p<0.10) or significantly associated with death according to univariate analysis (considering a p<0.20). The multicollinearity among covariates was also explored and taking a variance inflactory factor over 2 as criterion, the BMI was excluded having a high collinearity with waist circumference (=4.68). We also ran the same analyses investigating the association between the severity of liver steatosis (categorised as absent, mild, moderate, severe) and mortality. In all the analyses, people with no liver steatosis were taken as reference and the Cox's regression analysis data are reported as HRs with 95% CIs. A similar analysis was run taking cardiovascular or cancer death as outcome and censoring people died for other causes or for cancer/cardiovascular death, respectively.

All the analyses were performed using SPSS V.17.0 for Windows. All statistical tests were two-tailed and statistical significance was assumed for a p<0.05.

RESULTS

Sample selection

The MICOL III study initially included 1708 participants. After excluding 20 participants since they did not make the liver echography, 52 not having information regarding their alcohol intake, 17 with liver cirrhosis, 95 with a history of cancer and 79 without data regarding mortality status (lost at follow-up), we included 1445 participants in our analysis.

General characteristics

In the sample as whole, the mean age was 65.2±9.5 years (range: 40–89) and the women were the 44.2% of the whole population. The study subjects' characteristics by presence of liver steatosis and their alcohol intake are reported in table 1.

Participants with liver steatosis and low alcohol intake (ie, NAFLD) (n=457) did not differ in terms of age, percentage of females or smokers than those not having liver steatosis and low alcohol intake (n=596). Even if the mean BMI was similar between the two groups (p=0.84), participants with NAFLD had a significant higher waist circumference and higher values in both systolic and diastolic blood pressure (p<0.0001 for all comparisons). Conversely, no differences in terms of comorbidities were evident between the participants with NAFLD and those without (table 1).

People with AFLD (ie, high alcohol intake and liver steatosis) (n=228) did not differ in terms of age, percentage of females, smoking habits, blood pressure or comorbidities than those with no AFLD (n=164), even if the waist circumference was significantly higher in people with AFLD (p<0.0001) than those without (table 1).

Liver steatosis and mortality

After a median period of 12 years, 312 participants (=21.6% of the baseline population) died. The overall incidence was 19 (95% CI 17 to 21) per 1000 persons-year. Of them, 95 died for cardiovascular conditions, 67 for cancer and 150 for other reasons.

Table 2 shows the association between liver steatosis and mortality by alcohol intake. After adjusting for 10 potential confounders at baseline (age, gender, demographics, comorbidities), the presence of steatosis was not associated with any increased risk of death for both NAFLD (HR=1.15; 95% CI 0.87 to 1.51; p=0.33) and AFLD (HR=1.24; 95% CI 0.77 to 2.01; p=0.38). We further investigated whether the severity of liver steatosis was associated with higher mortality rate. After adjusting for potential confounders, while greater severity of liver steatosis was not associated with a higher risk of mortality in NAFLD, the presence of moderate liver steatosis increased the risk of overall death of more than two times (HR=2.16; 95% CI 1.19 to 3.91; p=0.01) in AFLD (table 2).

In all the analyses, people without evidence of liver steatosis were taken as reference. Incidence rates are reported per 1000 persons-year with their 95% CIs. The data are reported as HRs and 95% CIs after adjusting for age, sex, smoking status (current/previous vs never), presence of diabetes, acute myocardial infarction (all yes vs no); waist circumference, systolic and diastolic blood pressure, daily energy (all as continuous).

Table 3 reports the data regarding the association liver steatosis and specific-cause mortality, namely death due to CVD or cancer, after adjusting for potential confounders. Again, while the presence and the severity of NAFLD were not associated with CVD or cancer death, the presence of moderate degree of liver steatosis significantly increased the risk of death related to cancer in AFLD (HR=3.54; 95% CI 1.16 to 10.87; p=0.03).

In all the analyses, people without evidence of liver steatosis were taken as reference.

Table 1 Demographic and other characteristics of the study subjects by presence or not of liver steatosis and by alcohol intake

	NAFLD*			AFLD†		
	No (n= 596)	Yes (n=457)	P value‡	No (n=228)	Yes (n=164)	P value‡
Age (years)	65.3 (9.8)	66.3 (9.6)	0.11	63.6 (8.6)	64.1 (8.6)	0.53
Females (%)	54.4	57.6	0.30	14.1	13.0	0.78
Smokers (previous/actual) (%)	39.1	37.4	0.58	63.9	62.1	0.76
BMI (kg/m²)	29.9 (5.4)	29.9 (5.8)	0.84	29.3 (5.1)	29.4 (4.7)	0.95
Waist (cm)	93.7 (13.4)	97.1 (12.1)	<0.0001	96.3 (12.2)	100.1 (11.4)	<0.0001
Systolic blood pressure (mm Hg)	120.9 (20.9)	127.9 (19.0)	<0.0001	121.7 (20.2)	124.7 (18.9)	0.09
Diastolic blood pressure (mm Hg)	72.6 (10.2)	76.9 (9.3)	<0.0001	73.9 (9.6)	75.8 (12.9)	0.12
Daily energy intake (kcal)	2057 (860)	2068 (782)	0.83	2520 (695)	2592 (801)	0.33
Daily alcohol intake (g)	6.6 (7.6)	6.9 (7.4)	0.49	51.7 (21.3)	50.3 (20.8)	0.51
Diabetes (%)	13.9	15.8	0.44	12.4	16.4	0.26
Hypertension (%)	50.2	56.3	0.05	39.8	45.5	0.27
Acute myocardial infarction (%)	4.9	4.6	0.89	4.1	6.3	0.37

Values are reported as mean (SD) (for continuous variables), or % for categorical ones.
*Alcohol consumption <30 g/day (men), <20 g/day (women).
†Alcohol consumption ≥30 g/day (men), ≥20 g/day (women).
‡P values were calculated using the independent T-test for continuous variables and χ^2 test for categorical ones.
BMI, body mass index.

All the data are reported as HRs with their 95% CIs, adjusted for age, sex, smoking status (current/previous vs never), presence of diabetes, acute myocardial infarction (all yes vs no); waist circumference, systolic and diastolic blood pressure, daily energy (all as continuous).

DISCUSSION

Summary of findings

In our study, during a median follow-up period of 12 years, we failed to find any significant association between the presence and severity of liver steatosis and mortality NAFLD, while, when limited to AFLD, the presence of moderate liver steatosis increased the risk of overall death of more than two times as well as this condition increased the risk of cancer-related death.

Comparison with previous studies and novelty of our research

Overall, we have a limited knowledge if the presence of liver steatosis can increase per se the risk of mortality. One large study reported an increased risk of death among patients who had been admitted to the hospital and had a discharge diagnosis of fatty liver, but these findings are limited since the authors did not adjust for any potential confounder.[18] On the contrary, two studies, including liver biopsy registries for identifying the presence of fatty liver disease found that the incidence of mortality was similar in those with fatty liver and general population.[19 20] Another study following 144 patients with biopsy confirmed that NAFLD had similar survival probability than general population.[21]

However, all these studies explored the association between NAFLD and mortality in selected patients (eg, doing a biopsy for elevated liver enzymes or hospitalised), while NAFLD is highly prevalent in the general population. To our knowledge, only four cohort studies have evaluated the association between NAFLD and mortality in samples from the general population.[14 22–24] Three studies[19–21] used liver enzyme levels as surrogate markers of NAFLD, consequently having an important bias in these findings and another one used an echographic method as we did.[14] While the studies doing the diagnosis of NAFLD with raised liver enzyme levels found a higher risk of death in these people, the only study using the echography did not. Altogether, these finding probably suggest that only when liver has a certain grade of dysfunction can increase the risk of mortality. In this regard, one hypothesis can be the ability of the liver to regenerate in presence of steatosis given by the accumulation of triglycerides[25] thus limiting the damage of liver and consequently not having any impact on mortality. Even if liver steatosis are followed by some important complications, it is estimated that only a few people will have them, that is, about one person over 10 having NAFLD will have a NASH and of them the incidence of liver cancer is estimated between 0% and 12%.[26] Only recently a large study made in 318 224 people in Korea

Table 2 Association between liver steatosis and mortality by alcohol consumption

	NAFLD*					AFLD†				
	Incidence	Unadjusted HR	P value	Fully adjusted HR	P value	Incidence	Unadjusted HR	P value	Fully adjusted HR	P value
Absence of steatosis	18 (15–22)	1 (reference)	–	1 (reference)	–	15 (12–21)	1 (reference)	–	1 (reference)	–
Presence of steatosis	21 (18–26)	1.19 (0.91–1.55)	0.21	1.15 (0.87–1.51)	0.33	21 (15–28)	1.27 (0.80–1.99)	0.31	1.24 (0.77–2.01)	0.38
Mild	22 (17–29)	1.19 (0.85–1.67)	0.31	1.09 (0.77–1.54)	0.63	19 (11–32)	1.06 (0.56–2.02)	0.86	0.92 (0.47–1.79)	0.81
Moderate	21 (16–29)	1.25 (0.87–1.79)	0.23	1.38 (0.96–2.00)	0.09	25 (16–39)	1.64 (0.96–2.81)	0.07	2.16 (1.19–3.91)	0.01
Severe	19 (11–31)	1.01 (0.58–1.77)	0.96	0.87 (0.49–1.53)	0.62	11 (4–35)	0.72 (0.22–2.33)	0.58	0.59 (0.18–1.97)	0.39

*Alcohol consumption <30 g/day (men), <20 g/day (women).
†Alcohol consumption ≥30 g/day (men), ≥20 g/day (women).

reported a significant association between NAFLD and mortality (all-cause and specific), but these findings were significant only in women and, surprisingly, in obese men, NAFLD was associated with a reduced risk of death from cancer.[27] As correctly observed by Dr Stefan in an Editorial, it is likely that women involved in this study and having NAFLD clearly had a higher cardiometabolic risk profile, which might have increased the power to detect relationships of NAFLD with mortality.[28]

Finally, to the best of our knowledge, our study is the first exploring the association between liver steatosis and mortality in people having AFLD. Since the consumption of alcohol is overall increasing,[29] the finding that the presence of moderate liver steatosis can significantly increase the risk of death (in particular for cancer) indicates that people having high alcohol intake should be routinely screened for liver steatosis in order to prevent the transition to moderate forms. We can probably justify the lack of the association between severe forms and death due to the limited number of people having this condition. Thus, other studies are necessary to confirm our findings.

Limitations

The findings of our study should be interpreted within its limitations. First, although liver biopsies and nuclear MRI are the methods of choice for diagnosis of liver steatosis, ultrasonography is currently the preferred method for screening asymptomatic patients with suspected liver injury.[30] Several studies have demonstrated that the sensitivity, specificity and positive predictive value of ultrasound in detecting liver steatosis ranged widely (60%–94%) depending on the population chosen for study.[31 32] Taking into account for the ethical concerns, we could not perform liver biopsy of our patients. Second, the number of people with severe grade of either AFLD/NALFD are small and this could affect our results. Third, contrary to our expectations, BMI was not different between people having or not NAFLD. We can hypothesise that, in our study, only abdominal obesity is strictly associated with the presence of NAFLD, while obesity per se no, further confirming a peculiar association between waist circumference and this condition.[33] Fourth, we do not have information regarding liver enzymes and the calculation of markers of liver fibrosis (such as aspartate transaminases/alanino transaminase (AST/ALT) ratio or Fib-4) was not possible. Finally, the information regarding comorbidities are self-reported and this could introduce another bias such as we do not have any complete information regarding medications that, on the contrary, may significantly alter the association between liver steatosis and mortality.

Table 3 Association between liver steatosis and specific-cause mortality by alcohol consumption

	NAFLD*				AFLD†			
	CVD death	P value	Cancer death	P value	CVD death	P value	Cancer death	P value
Absence of steatosis	1 (reference)	–	1 (reference)	–	1 (reference)	–	1 (reference)	–
Presence of steatosis	0.83 (0.48–1.42)	0.49	1.17 (0.66–2.09)	0.59	1.21 (0.55–2.67)	0.64	1.61 (0.62–4.18)	0.33
Mild	0.47 (0.19–1.11)	0.09	1.24 (0.61–2.50)	0.55	0.97 (0.31–3.04)	0.96	0.67 (0.14–3.24)	0.62
Moderate	1.05 (0.51–2.13)	0.90	1.26 (0.58–2.74)	0.56	2.26 (0.89–5.74)	0.09	3.54 (1.16–10.87)	0.03
Severe	1.34 (0.57–3.12)	0.50	0.82 (0.24–2.76)	0.75	Not possible	–	1.06 (0.13–8.83)	0.96

*Alcohol consumption <30 g/day (men), <20 g/day (women).
†Alcohol consumption ≥30 g/day (men), ≥20 g/day (women).
CVD, cardiovascular disease.

CONCLUSION

Our study suggests that liver steatosis is not associated with any increased risk of death in NAFLD, while in AFLD moderate stages increased the risk of death, particularly for cancer-related death. Our findings suggest that other factors are probably more important in people with NAFLD for explaining their elevated rate of mortality, while a stricter ecographic follow-up should be proposed to people introducing high levels of alcohol. Since fatty liver disease is a common condition and continuously increasing, other longitudinal studies are needed to confirm/refute our findings.

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Contributors MGC and NV designed the study and wrote the paper. MN, RD and VG interpreted the data. AMC, RR, RI, RG, OR, VT and GDL enrolled the subjects. AL, CB and GL analysed the data. MC performed biochemical analyses and ultrasound ecography. GM and AO conceived the study. GL and GM gave critical revisions to the final draft.

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Competing interests None declared.

Patient consent for publication Not required.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Technical appendix, statistical code, and datasets are available from request to the corresponding author, upon reasonable request. The data are deidentified and they are available, upon reasonable request, to Nicola Veronese and Maria Gabriella Caruso, under the written permission of the Institute.

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