Editorial Commentary

Fatty liver disease and risk of all cause and cause-specific mortality outcomes in the older population

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Accumulating evidence in recent years has reinforced the notion that non-alcoholic fatty liver disease/metabolic dysfunction-associated fatty liver disease/metabolic dysfunction steatotic liver disease (NAFLD/MAFLD/MASLD) is a multisystem disease that increases the risk of all-cause and disease-specific mortality (1,2). Consequently, screening for the presence of fatty liver disease (FLD) in people who have metabolic comorbidities is recommended by various guidelines (3,4). The implementation of such an approach is challenging and very costly in elderly populations, not least because of the very high prevalence of metabolic abnormalities in this group. Screening whole populations of individuals is not likely to be cost-effectiveness if a high percentage of those individuals have evidence of FLD but are at low risk of consequent morbidity or mortality. Ageing, male sex and menopausal status are crucial risk factors for FLD and co-morbid metabolic conditions such as type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) (5-7). Moreover, evidence is now accumulating that ageing, sex and menopausal status can modify the association between FLD and mortality risk and FLD-associated risk of metabolic conditions such as T2DM (5-7). In *Table 1*, we have described the key studies to date that have investigated the modifying effect of age on the association between presence of NAFLD/FLD and all-cause mortality.

In the largest study to date to investigate the influence of older age on the association between FLD and mortality outcomes van Kleef *et al.* explored the relationship between FLD and all-cause and cause-specific mortality in an older age (≥65 years) population (8). This study included participants (n=4,093) from The Rotterdam Study which were predominantly of European ancestry (98.1%) with a mean age of 74.4±6.6 years and included a good representation of both sexes (42.7% men). Using ultrasound, the authors found that of the 4,903 participants, 1,508 were found to have hepatic steatosis (i.e., FLD). Participants were enrolled from 2009 to 2014 and were followed to 2018 (median follow-up 6.9 years) during which time 793 participants had died (29.6 per 1,000 person-years). In their fully adjusted model (which adjusted for age, sex, education, smoking status, alcohol consumption,

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Table 1 Studies indicating the modifying effect of age on the association between presence of NAFLD/FLD and all-cause mortality

Study	Age (median follow-up), years	Cohort/subset	Risk of all cause morality, aHR (95% CI)
Dunn *et al.*, 2008 (5)	45–54 (8.3)	No suspected NAFLD (n=1,114); suspected NAFLD (n=239)	4.14 (1.26–13.58)*
	55–84 (8.3)	No suspected NAFLD (n=3,598); suspected NAFLD (n=352)	1.26 (0.76–2.06)
Golabi *et al.*, 2019 (6)	60–74 (16.5)	No NAFLD (n=1,122); NAFLD (n=973)	1.23 (1.07–1.42)*
	75+ (7.5)	No NAFLD (n=715); NAFLD (n=461)	1.12 (0.97–1.29)
van Kleef *et al.*, 2023 (8)	65+ (6.8)	No FLD (n=2,585); FLD (n=1,508)	0.87 (0.73–1.03)

*, significantly different (P<0.05) compared to reference group (i.e., no NAFLD). NAFLD, non-alcoholic fatty liver disease; FLD, fatty liver disease; aHR, adjusted hazard ratio; CI, confidence interval.

components of metabolic syndrome, heart failure, coronary heart disease and stroke), the presence of hepatic steatosis was not associated with a higher risk of all-cause mortality [adjusted hazard ratio (aHR), 0.87; 95% confidence interval (CI): 0.73–1.03]. Similarly, the presence of hepatic steatosis was not associated with increased all-cause mortality in any of the pre-specified subgroup analyses and was not associated with cancer-related mortality (aHR, 0.77; 95% CI: 0.51–1.16) or cerebrovascular or cardiovascular mortality (aHR, 0.90; 95% CI: 0.54–1.50). These findings were consistent even when the authors stratified subjects by the presence or absence of MAFLD. Moreover, the findings were also similar to those obtained when the authors only corrected for age and sex, indicating that their findings were not a result of controlling for many parameters closely associated with FLD in their fully adjusted models. In a subset of participants (n=2,584), the authors also found that liver stiffness (LS) [assessed using vibration-controlled transient elastography (VCTE)] measurements were not associated with increased all-cause mortality even in those with both hepatic steatosis and an LS of ≥8.0 kPa compared to those without steatosis and lower LS measurements (aHR, 1.11; 95% CI: 0.65–1.89).

This is the largest prospective study to date to examine the relationship between FLD and mortality outcomes within a community-dwelling elderly population with a reasonably large event rate (749 events) over the 6.9-year follow-up period (26,765 person-years). However, it is important to consider that these observations predominantly pertain to a white Northern European population and the ultrasound method for detecting liver steatosis lacks sensitivity to detect lesser degrees of steatosis (i.e., <33%) (9). Thus, there may be misclassification bias as subjects in the control (non-FLD) group could have had undetected mild hepatic fatty infiltration (i.e., 5–32%) and may have been misclassified as not having FLD. Such bias would always attenuate the strength of any association towards the null. To their credit, the authors have acknowledged that whilst the fatty liver index-based liver steatosis assessment in their sensitivity analysis confirmed their ultrasound-based findings, this approach is also not able to distinguish between steatosis grades. Moreover, the aetiology of FLD within this cohort was demonstrably a group of subjects with MAFLD. Consequently, the authors were unable to explore whether FLD from different aetiologies (e.g., alcohol-related) was associated with increased mortality in this cohort.

The absence of any association between FLD and mortality outcomes in this study may also be explained by healthy survivor bias. Similarly, the duration of the exposure to risk factors such as FLD, and metabolic syndrome characteristics, may also powerfully influence the association between the key exposure (FLD) and mortality outcomes. It is feasible that a short duration of FLD in an older population may be insufficient time to influence the risk of mortality outcomes. That said, these issues do not detract from the observation that this investigated population contains individuals whose survival is not influenced by the presence of FLD and this questions the clinical importance of screening for FLD in this population type (10). That said, whilst screening for hepatic steatosis in all elderly people is of questionable clinical utility, liver fibrosis severity is most strongly associated with increased risk of mortality in patients with NAFLD/MAFLD/MASLD (11-13). In the study by van Kleef *et al.*, only a small proportion of participants (n=283, 11% of those with LS measurements) had an LS measurement of >8.0 kPa [≥8.2 kPa has been shown to be equivalent to clinically significant or ≥F2 liver fibrosis (14)] and 73 (26%) of these individuals did not have evidence hepatic steatosis. Consequently, one may question

whether the study sample had sufficient power to detect a statistically significant association between clinically significant liver fibrosis (or advanced liver fibrosis) and increased mortality. This limitation is perhaps exacerbated by the author's use of a >8.0 kPa cutoff within their analysis which is below the threshold for prediction of clinically significant liver fibrosis (see above) and advanced fibrosis [≥ F3 or ≥9.7 kPa (14)]. Moreover, whilst the authors indicate that similar results were observed using a higher kPa threshold (>10 kPa), it is likely that very few participants fell into this category, thus amplifying the potential influence of lack of sufficient power to detect an association.

Whilst we have highlighted some of the important limitations of the work by van Kleef and colleagues, it is important to recognise the findings in this study are consistent with those of other smaller previous studies (*Table 1*). In 2008, Dunn *et al.* suggested that the presence of suspected NAFLD in participants aged between 45–54 years was associated with an increased risk of all-cause mortality (aHR, 4.14; 95% CI: 1.26–13.58) (5). In contrast, in participants between the age of 55–84 years, there was no association between the presence of suspected NAFLD and all-cause mortality (aHR, 1.26; 95% CI: 0.76–2.06). Similarly, in 2019, work from Golabi *et al.* also indicated that the presence of NAFLD in participants aged 60–74 years old was associated with an increased risk of all-cause mortality (aHR, 1.23; 95% CI: 1.07–1.42), whereas there was no association observed in older participants (age 75+ years) (aHR, 1.12; 95% CI: 0.97–1.29) (6). Whilst these two studies appear to support the modifying effect of age on the association between the presence of NAFLD and risk of all-cause mortality, it is important to note that these studies included a limited number of elderly participants and may be subject to challenges of insufficient statistical power.

What are the current areas of uncertainty that need addressing, and what can we learn? The results in this field are important and interesting and emphasise that further work is needed to test associations between both liver fat and liver fibrosis, and disease-specific outcomes in subjects across different age groups. Additionally, since T2DM is a very important risk factor for liver fibrosis, CVD, CKD and certain cancers, it is important to know whether specific subgroups of older people with metabolic dysfunction such as those with T2DM, who represent an easily identifiable sub-group, could be targeted for screening for FLD. Given that the event rate is likely to be high in older people with T2DM, it is plausible that screening for FLD could also be cost-effective in this sub-group. With the widespread use and availability of non-invasive biomarkers and VCTE and with testing for genetic polymorphisms that alter the severity of FLD, but which also modify the association between FLD and coronary artery disease, it should now be possible to obtain these comparative data in different age-stratified subgroups of men and women from different ethnic groups.

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References

1. Targher G, Tilg H, Byrne CD. Non-alcoholic fatty liver disease: a multisystem disease requiring a multidisciplinary

and holistic approach. Lancet Gastroenterol Hepatol 2021;6:578-88.
2. Byrne CD, Targher G. NAFLD: a multisystem disease. J Hepatol 2015;62:S47-64.
3. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update. J Hepatol 2021;75:659-89.
4. National Guideline Centre (UK). NICE Guideline, No. 49. Non-Alcoholic Fatty Liver Disease: Assessment and Management. London: National Institute for Health and Care Excellence (NICE), 2016.
5. Dunn W, Xu R, Wingard DL, et al. Suspected nonalcoholic fatty liver disease and mortality risk in a population-based cohort study. Am J Gastroenterol 2008;103:2263-71.
6. Golabi P, Paik J, Reddy R, et al. Prevalence and long-term outcomes of non-alcoholic fatty liver disease among elderly individuals from the United States. BMC Gastroenterol 2019;19:56.
7. Kim Y, Chang Y, Ryu S, et al. NAFLD improves risk prediction of type 2 diabetes: with effect modification by sex and menopausal status. Hepatology 2022;76:1755-65.
8. van Kleef LA, Sonneveld MJ, Kavousi M, et al. Fatty liver disease is not associated with increased mortality in the elderly: A prospective cohort study. Hepatology 2023;77:585-93.
9. Saadeh S, Younossi ZM, Remer EM, et al. The utility of radiological imaging in nonalcoholic fatty liver disease. Gastroenterology 2002;123:745-50.
10. van Kleef LA, Sonneveld MJ, de Knegt RJ. Reply: Is there survival bias? The etiologic analysis for the negative association between fatty liver and mortality in the elderly populations. Hepatology 2023;78:E31-2.
11. Ekstedt M, Hagström H, Nasr P, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology 2015;61:1547-54.
12. Angulo P, Kleiner DE, Dam-Larsen S, et al. Liver Fibrosis, but No Other Histologic Features, Is Associated With Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology 2015;149:389-97.e10.
13. Simon TG, Roelstraete B, Khalili H, et al. Mortality in biopsy-confirmed nonalcoholic fatty liver disease: results from a nationwide cohort. Gut 2021;70:1375-82.
14. Eddowes PJ, Sasso M, Allison M, et al. Accuracy of FibroScan Controlled Attenuation Parameter and Liver Stiffness Measurement in Assessing Steatosis and Fibrosis in Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology 2019;156:1717-30.

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