



The importance of age for liver-related mortality in patients with metabolic-dysfunction associated steatotic liver disease

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In the last four decades, the importance of non-alcoholic fatty liver disease (NAFLD) has increased as the etiology of cirrhosis in the world and associated hepatocellular cancer (HCC). Recently, the terminology has been changed to metabolic-dysfunction associated steatotic liver disease (MASLD) (1). Importantly, a recent validation of the criteria revealed that 99.5% of NAFLD patients in a large cohort of Sweden met the MASLD criteria (2). The authors concluded that previous natural history data can be used, limiting the need for new studies after the implementation of the new criteria and new terminology (2). It has been convincingly shown that patients with NAFLD have a significantly higher mortality compared to the general population of same age and sex (3,4). Most of the previous studies on the natural history of NAFLD were based on patients with histologically proven or confirmed steatotic liver disease (3-5). MASLD is increasingly diagnosed with imaging modalities and liver histology has been largely replaced by non-invasive methods (6).

In a recent paper of *Hepatology*, researchers from Hong Kong reported interesting results from a large cohort of NAFLD patients, demonstrating higher proportion of liver-related deaths with increasing age, particularly in women (7). Around 31,000 patients diagnosed with NAFLD between

2000 and 2021 had approximately 662,000 person-years of follow-up. Patients aged 70–79 and 80–90 years, had 5.1% and 5.9% liver-related mortality, compared with 3% or lower, in groups younger than 70 years of age (7). As could be expected in patients classified as NAFLD cirrhosis, liver-related mortality was the dominating cause of death in these patients, accounting for approximately 37% of the total number of deaths. Interestingly, the incidence of liver-related deaths was higher among males with NAFLD younger than 70 years but was higher in females in older age groups. These results are of importance and the results add to the existing knowledge in the field of MASLD. Studies of the natural history of elderly patients diagnosed with NAFLD are limited. In a previous study from the US, NAFLD patients were associated with increased risk of mortality for 60–74-year-old individuals, this risk was not increased in those older than 74 years (8). However, this was a much smaller study with around 3,200 patients and also with a shorter follow-up than in the current study, with a median follow-up time for the study cohort aged ≥ 60 of 12 years (8). Thus, the US study suffered from limited power and the study from Hong Kong seems to provide more convincing results in this important context. The impact of age on the risk of liver-related mortality in

patients with NAFLD is of major importance due to longer life expectancy in the general population and the current growth of obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome globally. Indeed, a recent modeling study suggested a substantial increase in the prevalence of non-alcoholic steatohepatitis (NASH) by 15–56% and that associated liver-related mortality, decompensated liver disease and HCC would double as a result of an aging and/or increasing population (9). As pointed out by the authors of the current study, according to clinical guidelines from the European Association for the Study of the Liver (EASL), screening for NAFLD should be undertaken in patients older than 50 years of age with T2DM and/or metabolic syndrome but the cut-off for screening beyond a certain age is not clear and was not considered in these guidelines (9). In recent studies on the etiology of cirrhosis, the proportion of patients with cirrhosis due to viral hepatitis decreased in Sweden (10) and proportion of NAFLD-induced cirrhosis increased and in Italy, proportions of people with cirrhosis due to alcohol consumption and hepatitis C virus (HCV) decreased, whereas the proportion of people with cirrhosis due to NAFLD increased (11). However, in these studies the age of the different etiologies was not particularly investigated. However, in recent prospective studies from Iceland, it was demonstrated that patients who were diagnosed with cirrhosis due to NAFLD were significantly older than patients with other etiologies (12,13). Interestingly, the mean age at diagnosis of alcoholic liver disease (ALD)-*vs.* NAFLD-cases was 58 *vs.* 64 years in 2010–2015 (12), and during the last 7 years [2016–2022], the mean age was 59 years in patients with ALD and 68 years in NAFLD patients (13). Thus, it seems obvious that many of these patients will have liver-related outcomes in their 70s or 80s and the results of the current study are therefore extremely relevant. Coming back to the current study from Hong Kong, the strengths have been mentioned above, which are mainly a large cohort with a long duration of follow-up. However, as other retrospective studies it has important limitations that have to be taken into consideration. Although, the authors have tried as much as possible to exclude other chronic liver diseases as etiologies, no validation has been undertaken from the cohort on the accuracy of the International Classification of Diseases (ICD)-codes given. The main differential diagnosis is obviously alcoholic fatty liver disease (AFLD) and according to the authors, “excessive use of alcohol was based on nursing assessment form or the ICD-9-CM diagnosis codes” (7). Thus, it is conceivable that some of

the patients classified as NAFLD might have had ALD or a combination of obesity/metabolic syndrome and alcoholic overconsumption. Among the overall 45,293 patients receiving an ICD-code of fatty liver, only 567 (1.3%) patients were excluded due to excessive use of alcohol. This seems to be a low proportion of patients excluded for the main differential diagnosis. Another intriguing result in the Hong Kong NAFLD cohort, that a total of 9.3% had cirrhotic complications. Furthermore, in all age groups from <50 years and other age groups, 50–59, 60–69, 70–79, and 80–89 years, had 10–11% cirrhosis frequency.

The relative high cirrhosis frequency can be compared with original population-based studies of patients with NAFLD. In an early study from Olmsted County, Minnesota (3), among 420 NAFLD patients, only 5% were diagnosed with cirrhosis, although with somewhat shorter follow-up (mean of 7.6 years) than in the current study. Similarly, in a Swedish study (4) of biopsy-proven NAFLD patients, with a mean follow-up of approximately 14 years, 5.4% developed cirrhosis. Thus, in the current study almost twice as high proportion of patients developed cirrhosis than in the US and Swedish studies (3,4). In two other studies with biopsy-confirmed steatotic liver disease (14,15), comparing NAFLD patients and patients with alcoholic-induced steatosis, the development of cirrhosis was much higher in those with alcoholic fatty liver (AFL) than in NAFLD patients. In a study from Denmark, with around 20 years of follow-up, 22% of AFLD patients developed cirrhosis *vs.* only 1.2% among NAFLD patients (14). Similarly, in an Icelandic study, 20% developed cirrhosis in the AFLD group, although 7% of the NAFLD patients were diagnosed with cirrhosis, after a mean follow-up of 9 years (15). Thus, it is conceivable that in the large cohort of NAFLD-diagnosed patients in Hong Kong, a combination of factors of the metabolic syndrome and overconsumption of alcohol might have influenced their chronic liver disease development.

The top three causes of death in the current total study cohort were pneumonia, extrahepatic cancer, and cardiovascular disease (7). Comparison with the general population was not revealed in the paper. The high proportion of deaths from pneumonia was surprising. In the general population of Iceland, the most common causes of death per 100,000 inhabitants, from 2010 to 2021 were extrahepatic cancers, cardiovascular disease, cerebrovascular disease, Alzheimer’s disease, chronic obstructive pulmonary disease, accidents, and on the seventh place were influenza

and pneumonia together (<https://island.is/s/landlaeknir>). It is unclear why pneumonia was such a common among NAFLD patients in Hong Kong and requires further study.

In summary, the proportion of patients dying from liver disease was highest in patients aged 70 to 80 years. Thus, it seems clear that the relative importance of liver-related mortality increases with age in Hong Kong. Although not a high proportion of deaths, liver disease was the sixth leading cause of death in NAFLD patients aged 70–80 years. Furthermore, patients who developed cirrhosis, liver disease was the leading cause of death.

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