Cause of death by fibrosis stage in 959 patients with biopsy-proven NAFLD

We have read with interest the study from Simon *et al*, where the authors observed a higher mortality rate among patients with biopsy-proven nonalcoholic fatty liver disease (NAFLD) compared with reference controls without NAFLD.[1] Importantly, mortality rates exhibited a significant increase as the severity of NAFLD worsened, that is, from simple steatosis, non-fibrotic nonalcoholic steatohepatitis (NASH), non-cirrhotic fibrosis (ie, F1–F3, with or without NASH) to cirrhosis. The leading causes of death were attributable to extrahepatic cancers and liver cirrhosis, while cardiovascular disease and hepatocellular carcinoma had a comparatively lesser impact. This extensive study of patients with NAFLD reveals higher mortality rates across different NAFLD stages but does not stratify causes of death within the respective pre-cirrhotic fibrosis stages (F0–F3). Owing to the long natural history of NAFLD, for example, patients with F0 and F1 may never experience liver-related events.[2–4] For that reason, to assess the distribution of causes of death based on fibrosis stage, we retrospectively leveraged the granular data from a cohort of 959 patients with biopsy-proven NAFLD.

The patients aged ≥18 years were enrolled from three university hospitals in Sweden between 1974 and 2020 (methods detailed in online supplemental appendix 1).[5] The median age at biopsy was 51 years (IQR 39–60). There were 222 (23.2%) patients with fibrosis stage 0, 372 (38.9%) with F1, 210 (21.9%) with F2, 100 (10.4%) with F3 and 55 (5.7%) with F4 (cirrhosis). Of all patients, 542 patients had NASH (table 1). While the median age at biopsy aligned closely, this cohort exhibited a lower proportion of women (38% vs 45%) compared with the study by Simon *et al*. In addition, this study showed a higher prevalence of diabetes (25% vs 11%), hypertension (69% vs 10%), hyperlipidemia (18% vs 7%) and obesity (40% vs 4%), reflecting the higher sensitivity to detect such comorbidities in this medical chart-based cohort compared with use of administrative coding. The proportion of cirrhosis was however consistent at approximately 5.7% in both cohorts.

During a median follow-up of 17.9 years, 335 (34.9%) out of 959 patients died, at a mean age of 74.6 years. All-cause mortality increased as the fibrosis stage worsened: 75 (33.8%) patients with F0, 120 (32.4%) with F1, 69 (32.7%) with F2, 45 (45%) with F3 and 26 (47.3%) with F4 died (p for trend=0.019). Liver-related mortality was the leading cause of death for patients with F4 (53.9%), followed by extrahepatic cancer (15.4%) (figure 1). In non-cirrhotic patients with NAFLD (F0–F3), liver-related mortality increased with the severity of fibrosis stage (8.0% in F0, 10.8% in F1, 14.5% in F2, 20.0% in F3, adjusted HR (aHR)=1. 90 (95% CI 1.32 to 2.73), p_{trend}=0.001). The aHR for liver-related mortality in patients with F1, F2 and F3 was 1.51 (0.56–4.02), 2.80 (1.00–8.00) and 6.62 (2.16–20.3), respectively, compared with those with F0 after adjusting for age, sex and metabolic risk factors However, among patients with F0–F2, death attributable to cardiovascular diseases and extrahepatic cancers were considerably more common than death from liver-related causes. For patients with F3, causes of death were similarly distributed between liver-related disease (20%), cardiovascular disease (20%) and extrahepatic cancer (24%).

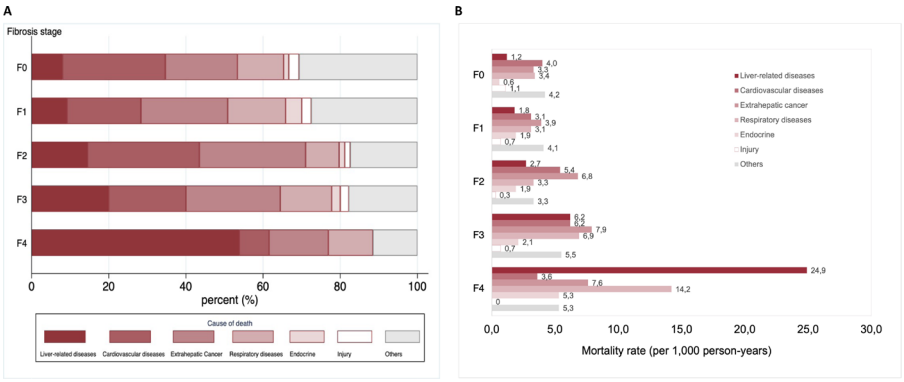

Figure 1 Proportions (A) and mortality rates (B) of cause-specific death by fibrosis stage.

Table 1 Baseline characteristics of patients with biopsy-proven NAFLD (n=959)

Baseline parameters	N (%)/median (IQR)
Age at biopsy (years)	51 (39–60)
Sex (female)	367 (38.3)
Follow-up time (years)	17.2 (7.5–28.0)
F0	222 (23.2)
F1	372 (38.9)
F2	210 (21.9)
F3	100 (10.4)
F4	55 (5.7)
NASH*	542 (31.7)
Cardiovascular disease	67 (7.0)
Type 2 diabetes	240 (25.0)
Hypertension	665 (69.3)
Hyperlipidemia	171 (17.8)
Extrahepatic cancer	77 (8.0)
Body mass index (kg/m^2)	28.9 (26.2–32.1)

*Data on NASH status is available in 846 patients.
NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

To summarise, among individuals with biopsy-proven NAFLD and cirrhosis, liver disease was the most common cause of mortality. Conversely, in patients with non-cirrhotic fibrosis, death from cardiovascular diseases and extrahepatic cancers surpassed liver-related diseases as the main causes of death, which was in contrast to the results from Simon *et al* where they found the contributions of cardiovascular disease were modest in patients with NAFLD. These results highlight that different management strategies and goals should be re-evaluated and prioritised in patient counselling to improve prognosis.

Ying Shang [1], **Camilla Akbari**,[2] **Maja Dodd**,[2] **Patrik Nasr** [3], **Johan Vessby**,[4] **Fredrik Rorsman**,[4] **Stergios Kechagias**,[3] **Per Stål**,[1,5] **Mattias Ekstedt**,[3] **Hannes Hagström** [1,5]

[1]Department of Medicine, Huddinge, Karolinska Institutet, Stockholm, Sweden
[2]Department of Medicine, Karolinska Institutet, Stockholm, Sweden

[3]Department of Gastroenterology and Hepatology and Department of Health, Medicine, and Caring Sciences, Linköping University, Linköping, Sweden
[4]Department of Gastroenterology and Hepatology, Uppsala University Hospital, Uppsala, Sweden
[5]Division of Hepatology, Department of Upper GI, Karolinska University Hospital, Stockholm, Sweden

Correspondence to Dr Ying Shang; ying.shang@ki.se

X Ying Shang @YingShang1 and Hannes Hagström @hanneshagstrom

Contributors Study concept and design: YS and HH. Acquisition of data: CA, MD, PN, JV, FR, SK, PS, ME and HH. Statistical analysis and drafting of manuscript: YS. Interpretation of data and critical revision: All authors.

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ORCID iDs
Ying Shang http://orcid.org/0000-0002-1496-1799
Patrik Nasr http://orcid.org/0000-0002-2928-4188
Hannes Hagström http://orcid.org/0000-0002-8474-1759

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