Editorial

The changing of natural history of nonalcoholic fatty liver disease (NAFLD): is advanced fibrosis the best predictor of long-term adverse outcomes?

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Nonalcoholic fatty liver disease (NAFLD) is currently the most common chronic liver disease observed in clinical practice both in developed and in developing Countries (1). NAFLD affects approximately 25–35% among general adult population, 70–75% among patients with type 2 diabetes (T2DM) and up to 95% among those with obesity (1).

The term NAFLD encompasses a spectrum of fat-related liver conditions, that includes simple accumulation of fat (fatty liver or steatosis), nonalcoholic steatohepatitis (NASH), advanced fibrosis and cirrhosis, with its specific clinical consequences, such as decompensated liver disease and hepatocellular carcinoma (HCC) (2,3). Although the prevalence of NAFLD in the general population is relatively high, the most patients with NAFLD have simple steatosis, which seems to be not associated with long-term adverse outcomes (1-3). However, it is estimated that approximately 5–10% of patients with NAFLD will develop NASH and that nearly 30–35% of these will progress to advanced fibrosis or cirrhosis over time (1-3). Importantly, the prevalence of these severe forms of NAFLD appears to be much higher in some high-risk patient groups. For instance, studies that used liver biopsy for detecting NAFLD documented that the prevalence of NASH and advanced fibrosis among patients with T2DM was roughly 65–70% and 30–40%, respectively (1-3).

Although it has become increasingly clear that NAFLD is a multi-systemic disease and that patients with NAFLD have an increased risk of overall, liver-related and cardiovascular mortality compared to those without NAFLD (4), in the last few years accumulating evidence has provided new data regarding the prognostic role of the distinct histological features of NAFLD (5-10). In particular, several studies seem to indicate that fibrosis stage, but no other histological features, is the strongest determinant of overall and disease-specific mortality in patients with NAFLD. For instance, in a recent cohort study including 229 well-characterized patients with biopsy-proven NAFLD followed for a mean period of 26.4 years, Ekstedt *et al.* reported that, compared to a sex- and age-matched reference population, overall mortality was not increased in patients with NAFLD activity score (NAS, a numerical score for histologically detecting the presence of NASH which is characterized by the sum of the separate scores for steatosis, hepatocellular ballooning and lobular inflammation, with the most NASH patients having a NAS score of ≥5) 5–8 and fibrosis stage 0–2, whereas patients with fibrosis stage 3–4, regardless of NAS, had an increased risk of overall and cardiovascular mortality (8). In another study of 256 patients with biopsy-proven NAFLD who were followed for a mean period of approximately 28 years, Söderberg *et al.* documented that, compared to the total Swedish population, patients with NAFLD had an increased risk of overall mortality [standardized mortality ratio (SMR), 1.69; 95% confidence interval (CI): 1.24–2.25] (9). Specifically, patients with mild steatosis had a 55% higher risk of overall mortality (SMR, 1.55; 95% CI,

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0.98–2.32), whereas those with moderate/advanced fibrosis had an 86% increased risk of mortality (SMR, 1.86; 95% CI: 1.19–2.76) (9). In a retrospective observational study of 619 patients with NAFLD, as detected by liver biopsy, Angulo *et al.* showed that, compared to those without fibrosis, patients with fibrosis (independent of NASH or NAFLD activity score) had a reduced survival as well as an increased risk of developing serious liver-related events, over a median follow-up period of 12.6 years (10). In addition, in a recent systematic review and meta-analysis of five unique, observational studies, enrolling approximately 1,495 biopsy-proven NAFLD patients with a total of 17,452 patient years of follow-up, Dulai *et al.* reported that, compared to NAFLD patients with no fibrosis (stage 0), NAFLD patients with fibrosis had an increased risk of overall mortality, and that such risk progressively increased according to the fibrosis stage [i.e., stage 1: mortality rate ratios (MRR) =1.58, 95% CI: 1.19–2.11; stage 2: MRR =2.52, 95% CI: 1.85–3.42; stage 3: MRR =3.48, 95% CI: 2.51–4.83 and stage 4: MRR =6.40, 95% CI: 4.11–9.95] (11). In that study, similar findings were also observed for the risk of liver-related mortality (11).

However, although the findings of meta-analysis and cohort studies provided consistent evidence regarding the natural history of NAFLD, it is important to underline that these studies lack of a sufficiently large sample or a long follow-up, thus making the estimates of the natural history of NAFLD somewhat inaccurate, as, notably, NAFLD is a slowly progressive disease in most cases.

Consistent with this background of evidence, the study of Hagström *et al.* [recently published in *Journal of Hepatology*, see ref. 12 (12)] adds a further critical piece of information by the documentation that the fibrosis stage, but not the presence of NASH, was the most robust predictor for overall and liver-specific morbidity and mortality in patients with NAFLD (12). In fact, in this recent retrospective cohort study involving 646 patients with biopsy-proven NAFLD and 6,345 age- and sex-matched controls, who were followed for a mean period of approximately 20 years, the investigators found that roughly 12% of patients with NAFLD and 2.2% of controls developed serious liver-related events (defined as an ICD-code for liver failure, cirrhosis, HCC or decompensated liver disease) (P<0.001) (12). Furthermore, the risk of developing serious liver-related events strongly increased in according to the fibrosis stage [hazard ratio (HR) ranging from 1.9 in F0 to 104.9 in F4], when compared to controls (12). Importantly, in that study, although patients with NASH had a small increase of the risk for liver-specific mortality, when compared to controls, this risk lost the statistical significant after adjustment for important confounders, including the fibrosis stage. In addition, in patients with comparable fibrosis stages, presence of NASH did not have a significantly effect on that estimates (12). Interestingly, the investigators also calculated that the minimum time of developing serious liver-related events was approximately 2 years in NAFLD patients with advanced fibrosis (F3, 6.0 years, 95% CI: 2.3–9.6 years), 9 years in those with fibrosis F2 (19.4 years, 95% CI: 9.3–29.5 years) and approximately 22–26 years in those with fibrosis F0–F1 (30.5 years, 95% CI: 21.5–39.6 years in F0; 35.6 years, 95% CI: 25.6–45.4 years in F1) (12). Notably, almost identical findings were observed for overall mortality (12).

Collectively, this evidence, based on biopsy-proven NAFLD, undoubtedly shows that fibrosis stage, independent of the presence/severity of other histologic features (including the presence of NASH or NAFLD activity score), is the strongest and best determinant of long-term prognosis in patients with NAFLD. Notably and importantly, this appears not only restricted to liver-related morbidity and mortality, but also extends to overall and cardiovascular mortality (4,13).

A possible explanation of these results could be found in the flaw of the NAFLD activity score, since the presence and grading of steatosis could have an inappropriate effect, when compared to lobular inflammation and ballooning, and, importantly, the portal inflammation (which is a very important histological feature) is not included in such score (14). On the other hand, lobular inflammation and ballooning could be an epiphenomenon comparable to simple steatosis and, therefore, not specifically linked to the activation of fibrogenic pathways (14).

The results of the study of Hagström *et al.* (12) strongly concur to change the assertion that NASH, but not simple steatosis, is associated with a poor long-term prognosis, contributing to focus the attention on the fibrosis stage rather than necro-inflammation and other histological features. However, it is important to point out that the presence of NASH and histopathologic features, other than fibrosis, may still contribute to the short-term disease progression, as suggested by some recent studies (15,16)

The changing paradigm in the natural history of NAFLD may have several clinical implications for the management and treatment of patients with NAFLD. In clinical practice, in fact, patients with NAFLD (especially when T2DM or

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obesity are present at the same time) should be routinely assessed for the presence of liver fibrosis with at least two non-invasive methods, such as biomarkers and elastography (17-19). If non-invasive methods suggest the high probability of fibrosis, this should be confirmed by liver biopsy (17-19). Based on the novel findings of the study of Hagström *et al.* (12), NAFLD patients with advanced fibrosis (stages 3 and 4) should be tightly monitored by health care providers to evaluate the development and progression of serious liver-related complications (12). Conversely, patients with NAFLD and moderate fibrosis (stage 2) should be re-examined within a period of no more than 10 years in order to detect individuals that have developed advanced fibrosis (12). Instead, patients with NAFLD and mild or no fibrosis (stages 0 and 1) should be re-examined for the development of progressive fibrosis within a period of approximately 20 years (12).

In addition, the definition of primary endpoints for measuring histologic effectiveness in NASH clinical trials should change and take into account that the NAS is not related with poor clinical outcomes, but that liver fibrosis is the strongest determinant of adverse long-term outcomes in these patients. To date, however, there are no approved pharmacological agents for the treatment of NAFLD, but some large phase III trials are getting underway [for a recent review about this issue see ref. 20 (20)]. An important outcome of these trials is the reduction of the fibrosis and the resolution of NASH. Although further studies assessing whether the resolution of NASH itself is associated with a reduction of overall and liver-related mortality are timely required, it is reasonable to speculate that it is unlikely that resolution of NASH without a specific effect on fibrosis will have a strong impact on the overall and disease-specific mortality in patients with NAFLD. Therefore, the next clinical trials in patients with NAFLD should mainly focus on the reduction of fibrosis, as detected by liver biopsy or magnetic resonance elastography.

To date, however, health care providers who manage these patients should highlight the importance of lifestyle changes, weight loss and physical activity as the central point of the treatment. Moreover, they also should assess and treat the individual components of the metabolic syndrome, such as dyslipidemia, hypertension, and insulin resistance (or T2DM). For patients with biopsy-proven NASH or advanced fibrosis, current medications with demonstrated benefit could be pioglitazone, vitamin E, liraglutide, or pentoxifylline.

In conclusion, based on available data (5-15), health care providers, managing patients with NAFLD, should keep in mind that the presence of fibrosis is directly related to long-term adverse outcomes (therefore, our capacity to identify patients at high risk of fibrosis will be crucial in the next future in order to find out who should be targeted for disease-modifying therapy when it will become available), while the presence of NASH and other histopathologic features (beyond the fibrosis) may still play a role in short-term disease progression.

The natural history of NALFD is changing and probably also our approach to this disease.

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Footnote

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