Editorial

# Nonalcoholic fatty liver disease with advanced fibrosis as a multi-systemic disease: proceed with caution

**Masato Yoneda, Yuji Ogawa, Kento Imajo, Atsushi Nakajima**

Department of Gastroenterology and Hepatology, Yokohama City University Graduate School of Medicine, Yokohama, Japan

*Correspondence to:* Atsushi Nakajima. 3-9 Fuku-ura, Kanazawa-ku, Yokohama 236-0004, Japan. Email: nakajima-tky@umin.ac.jp.

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Accompanying the current epidemics of metabolic syndrome (MS) and obesity caused by westernization of lifestyles, the incidences of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) have been increasing worldwide over the last few decades (1). Now, NAFLD has a global prevalence estimated at 25% of the world population, with some geographical; the highest prevalences are in the South America and Middle East. Namely, NAFLD has become recognized as the most common liver disease worldwide (2).

The natural history of NAFLD remains uncertain. NAFLD/NASH with fibrosis often leads to progression to cirrhosis and development to hepatocellular carcinoma (2,3), thus posing an important global health problem medically as well as socioeconomic perspective. NAFLD is also regarded as a liver component of MS and is associated with MS risk factors such as obesity, DM, and dyslipidemia (4,5). Recently, a growing body of evidence has been collected to support the notion that NAFLD should be treated as an early mediator of systemic diseases as well as a liver-specific disease.

In a multi-center cohort study investigated the long-term prognostic relevance of histologic feature of NAFLD by Angulo *et al.* in 2015, the advanced fibrosis of liver fibrosis was found to be correlated with the overall morality or the receipt of a liver transplantation (6). Hepatologists all over the world were surprised by the results of this study, since the largest cause of death among patients with NAFLD was found to be cardiovascular disease (CVD) followed by non-liver malignancies in their retrospective analysis of 619 NAFLD patients for median 12.6 years follow-up period. Liver-related mortality was the third cause of death in this study.

Recently [2018], Vilar-Gomez *et al.* reported that NAFLD patients who develop cirrhosis mainly experience liver-related events, whereas pre-cirrhotic patients (F3) exhibit mainly non-hepatic cancers and vascular events (7). Numerous epidemiological studies have suggested that NAFLD may be both a consequence and a cause of MS and its individual components. Furthermore, the link between NAFLD/NASH and hypertension, T2DM and atherosclerosis/CVD is considered to be multifarious than previously assumed (8). In addition, Sinn *et al.* indicated that there were significant associations between NAFLD and development of coronary artery calcium (CAC) independent of factors that associated with metabolic risk factors (9). Furthermore, it is indicted that the presence and severity of NAFLD independently predicts fatal/nonfatal CVD events in a long-term prospective studies (8).

Next, the strong relation between non-hepatic malignancy and NAFLD is also worthy of attention. As investigated in a study by Vilar-Gomez *et al.* (7), a relationship between colorectal cancer (CRC) and NAFLD has been frequently reported. In a review of 11 studies examining over 90,000 asymptomatic adults who were undergoing a colonoscopy, Mantovani *et al.* found that the incidence of colorectal adenomas and CRC is on the rise with the presence of NAFLD. Furthermore, the fibrosis severity of NAFLD was related to a significantly increased risk of prevalent CRC (10).

In summary, NAFLD should be recognized as a precursor of MS and multisystem disease affecting extrahepatic organs. There are several diseases in which

**Table 1** Nonhepatic complications associated with NAFLD/NASH

| Variable | Non-hepatic complications | |
|---|---|---|
| | Diseases associated with progression of NAFLD pathogenesis (causes) | Diseases in which NAFLD is associated with their progression (results) |
| Brain | Hypopituitarism, adult growth hormone deficiency (AGHD), sleep disorder, anorexia nervosa, antipsychotics | Major depression, sleep disorder, dementia |
| Oral cavity, pharynx | Periodontal disease | Oropharyngeal cancer |
| Circulation | Antiarrhythmic drug | Coronary artery stenosis, ischemic heart disease, cardiac hypertrophy, left ventricular diastolic dysfunction, arrhythmia |
| Respiration | Sleep apnea syndrome (SAS), obstructive pulmonary disease (COPD) | Lung cancer |
| Gastroenterology | Pancreaticoduodenectomy | Reflux esophagitis, functional dyspepsia, esophageal/gastric/colorectal/pancreatic cancer |
| Kidney | – | Chronic kidney disease (CKD), renal cancer |
| Female genitalia | Menopause, polycystic ovary syndrome (PCOS) | Sterility, ovarian, uterine cancer |
| Locomotorium | Locomotive syndrome, lipodystrophy | Osteoporosis |

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

NAFLD is associated with their progression and vice versa (*Table 1*). The results of the study by Vilar-Gomez *et al.*, are directly relevant to patient management, counseling and monitoring. Based on their findings, NAFLD patients with advanced fibrosis and cirrhosis should receive adequate surveillance for hepatocellular carcinoma, whereas the cardiovascular health of pre-cirrhotic patients (F3) should be closely monitored to prevent CVD and non-hepatic malignancy. Evaluation of hepatic histology which can take from liver biopsy is the accepted golden standard for fibrosis staging of NAFLD in guidelines from the Japanese Society of Gastroenterology (JSG), the guidance from the American Association for the Study of Liver Disease (AASLD) and European guidelines from the European Association for the Study of the Liver (EASL) (11-13), though it is an invasive examination, has a selection bias inherent to liver biopsy, and is impractical for the repeated assessment of liver tissue conditions. The reliable non-invasive methods such as US/MRI-based elastography for the assessment of fibrosis stage of the liver have become essential to the treatment of NAFLD (14,15).

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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