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Risk difference of liver-related and cardiovascular events by liver fibrosis status in nonalcoholic fatty liver disease

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Keywords

nonalcoholic fatty liver disease (NAFLD); hepatocellular carcinoma (HCC); decompensation; cardiovascular disease (CVD); magnetic resonance elastography (MRE)

Nonalcoholic fatty liver disease (NAFLD) has affected more than one-fourth of the global population, thus emerging as a worldwide health and economic burden[1]. The common causes of death in patients with NAFLD include cardiovascular disease (CVD), decompensation, and hepatocellular carcinoma (HCC). However, identifying the risk of these complications in patients with NAFLD remains an unmet need in clinical practice.

Liver fibrosis is significantly associated with mortality risk in NAFLD[2], and a significant association between magnetic resonance elastography (MRE) and liver fibrosis has been reported. However, the association between MRE and complication incidence (HCC, decompensation, and CVD) remains unclear. Hence, in this study, we investigated the association between MRE and the development of HCC, decompensation, and CVD in patients with NAFLD.

This is a retrospective cohort study comprising patients with NAFLD who underwent liver stiffness measurement by MRE between April 2015 and October 2020 at Musashino Red

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Author contribution: Study conception: NT, MH, MK, NI. Data collection: NT, MH, MK, KI, SK, KY, SS, YH, LO, KT, CM, SK, YY, YT, KT, HN, JI, and NI. Data analysis: NT, MH. Manuscript drafting: NT, MK, NI. Clinical revision: MK, RL, NI. Obtained funding: NT, MK, RL. Study supervision: MK, RL, NI. All authors read and approved the final version of the manuscript.

Ethical approval: The study protocol was approved by the clinical research ethics committee of the Musashino Red Cross Hospital and conformed to the ethical guidelines of the Declaration of Helsinki (approval number: 2007).

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Cross Hospital. All patients underwent MRE as a part of their routine clinical evaluation and received standard of care. NAFLD is defined as the presence of fatty liver on imaging modalities or having hepatic steatosis index of >30[3]. The study observation started at the time of MRE evaluation. The primary outcome was the incidence of HCC, decompensation, and CVD. Written informed consent was obtained from each patient. The study protocol was approved by the clinical research ethics committee of the Musashino Red Cross Hospital and conformed to the ethical guidelines of the Declaration of Helsinki (approval number: 2007).

A total of 428 patients with NAFLD were enrolled in this study (Supplemental Table.1). The median (interquartile range [IQR]) age and MRE were 67 (56–74) years and 3.8 (2.6–6.0) kPa. Patients were stratified into three groups based on liver stiffness[4]: minimal fibrosis (MRE: <3 kPa, n = 139), moderate-advanced fibrosis (MRE: 3–4.7 kPa, n = 129), and cirrhosis (MRE: >4.7 kPa, n = 160). Generally, patients with cirrhosis were older and had a higher proportion of diabetes mellitus (DM) and hypertension. The median (IQR) follow-up periods were 1.9 (1.0–3.0) years, and during this time, new HCC, decompensation, and CVD development were observed in 10, 15, and 10 patients, respectively.

In cirrhosis patients, HCC incidence after 1, 2, and 3 years was 6.6%, 8.1%, and 9.8% and decompensation incidence was 2.7%, 8.5%, and 12.0%, respectively. HCC (Figure 1A, $p < 0.001$) and decompensation (Figure 1B, $p = 0.001$) incidence were significantly higher than minimal and moderate-advanced fibrosis. On the other hand, CVD incidence after 1, 2, and 3 years was 0%, 0.9%, and 0.9% in cirrhosis; 3.3%, 5.8%, and 5.8% in moderate-advanced fibrosis; and 2.6%, 2.6%, and 2.6% in minimal fibrosis, respectively (Figure 1C, $p = 0.06$). Between the cirrhosis and moderate-advanced fibrosis groups, CVD incidence was significantly higher for those with moderate-advanced fibrosis ($p = 0.01$).

The factors associated with HCC, decompensation, and CVD development were investigated using MRE as continuous values. In the multivariable analysis with adjusting age, gender, DM, dyslipidemia, and hypertension, MRE (per 1 kPa) was found to be a significant factor for HCC (hazard ratio [HR]: 1.37, 95% confidence interval [CI]: 1.1–1.7, $p = 0.01$, Supplemental Table.2), and decompensation (HR: 1.34, 95% CI: 1.1–1.6, $p = 0.001$), but not for CVD (HR: 0.71, 95% CI: 0.5–1.1, $p = 0.06$).

In this study, we demonstrated that the risk of HCC and decompensation incidence increased with an increase in MRE. On the other hand, CVD risk increased in patients with moderate-advanced fibrosis than those with cirrhosis. Based on the results of this study, more attention should be paid to HCC and decompensation development as MRE increases, but CVD risk should be paid in patients with moderate-advanced fibrosis.

Liver fibrosis is the most important prognostic factor in NAFLD, making its assessment crucial in clinical practice[2]. Previous studies were able to determine a significant association between MRE and decompensation development[5], but HCC development was not evaluated. In this study, the risk of HCC development increased as MRE increased, a pattern similar to that of decompensation risk.

Patients with NAFLD are at high risk for CVD development and CVD is a more prevalent cause of death[6]. However, in studies investigated biopsy-proven patients with NAFLD, the

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association between liver fibrosis severity and CVD is controversial[7,8]. Furthermore, there is no study to investigate the association between CVD and MRE. As we demonstrated in the study, the CVD risk with liver fibrosis severalty is not similar to the risk of HCC and decompensation. CVD risk increases as liver stiffness increases to moderate-advanced fibrosis, but CVD risk decreases with further increases to cirrhosis. This study provides new evidence on the association between CVD risk and liver stiffness, and CVD risk estimation by MRE may be useful for clinical practice.

In this study, all patients repeatedly received standard of care and medical assessment. However, this study was conducted at a tertiary center for liver disease, and, therefore, there are some selection and observation biases (relatively high liver stiffness, low prevalence of CVD at baseline, and shorter follow-up periods in minimal fibrosis patients). Furthermore, recent studies demonstrated the sex difference in NAFLD disease progression[9]. To address these biases and issues, further large-scale prospective multicenter cohort studies are needed.

In this study, we demonstrated the different association among HCC, decompensation, CVD and liver stiffness by MRE. These results provide an effective surveillance and medication strategy for HCC, decompensation, and CVD in patients with NAFLD. In patients with moderate-advanced fibrosis, CVD surveillance is needed, whereas in patients with cirrhosis, liver-related complications surveillance is needed and CVD risk surveillance may be lessened.

In conclusion, the risk of HCC and decompensation development increased with a greater increase in MRE. On the other hand, CVD risk increased to moderate-advanced fibrosis but decreased with cirrhosis. The risk of HCC, decompensation, and CVD development differ according to fibrosis status in patients with NAFLD.

Additional methods

Exclusion criteria

Patients with chronic hepatitis C and B, autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), significant alcohol consumption, or caused by medications were excluded. Hepatitis C virus (HCV) and hepatitis B virus (HBV) infection were defined by the identification of HCV RNA and HB surface antigen and/or HBV DNA. Significant alcoholic consumption was defined as >30 g and >20 g per week in men and women, respectively. AIH (the presence of antinuclear antibody and/or smooth muscle antibody) and PBC (combining alkaline phosphatase elevation, the presence of antimitochondrial antibody, and histological evaluation) were defined based on the American Association for the Study of Liver Diseases practice guidelines. Patients with follow-up periods <6 months were also excluded.

Liver stiffness by MRE

MRE was performed using a Signa HDxt 1.5T (GE Medical Systems, Waukesha, WI, USA) and MR Touch (GE Healthcare). In summary, the shear waves were generated by the external vibration of 60 Hz using a passive driver as the vibration device slightly placed to the right, lateral to the xiphoid process. Cross-sectional elastography images were created

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by the stiffness generated from the wave propagation information obtained by gradient echo sequence. The region of interest (ROI) was placed at the right hepatic lobe on each slice of the stiffness map, carefully avoiding the liver surface, liver edge, gallbladder, blood vessels, bile ducts, tumors, and artifacts. The mean stiffness value of three circular ROIs placed at different slices was used for the analysis. Patients were stratified into three groups based on liver stiffness: minimal fibrosis (MRE: <3 kPa), moderate-advanced fibrosis (MRE: 3–4.7 kPa), and cirrhosis (MRE: >4.7 kPa). The thresholds were based on those determined by a previous meta-analysis[4].

Primary outcome

The primary outcome was the incidence of HCC, decompensation, and CVD. All patients visited the outpatient clinic every 1–6 months. Ultrasonography and blood tests, including tests for tumor markers, were performed every 3–6 months for HCC surveillance. Decompensation was defined as the development of ascites, hepatic encephalopathy, or gastro-esophageal variceal bleeding. CVD was defined as the development of coronary heart disease, cerebrovascular disease, peripheral vascular disease, or heart failure. A history of HCC, decompensation, and CVD was observed in 59, 8, and 18 patients, respectively; these patients were excluded from each analysis.

Statistical analysis

Patient characteristics among the three groups were compared using Fisher's exact test or Kruskal–Wallis test. The cumulative incidence was evaluated using the Kaplan–Meier method, and the differences between groups were analyzed by the log-rank test. Univariable and multivariable Cox proportional hazards models were used to analyze the factors associated with HCC, decompensation, and CVD. On multivariable analysis, MRE was adjusted for age, gender, DM, dyslipidemia, and hypertension. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Shimotsuke, Japan), a graphical user interface for R version 3.2.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of Interest:

Namiki Izumi received lecture fees from Gilead Sciences Inc., and Abbvie. Masayuki Kurosaki received lecture fees from Gilead Sciences Inc., Abbvie, Eisai Co., Ltd., Bayer AG, Otsuka Holdings Co., Ltd. Rohit Loomba serves as a consultant or advisory board member for Alnylam/Regeneron, Arrowhead Pharmaceuticals, AstraZeneca, Bird Rock Bio, Boehringer Ingelheim, Bristol-Myer Squibb, Celgene, Cirius, CohBar, Conatus, Eli Lilly, Galmed,

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Gemphire, Gilead, Glympse Bio, GNI, GRI Bio, Inipharm, Intercept, Ionis, Janssen Inc., Merck, Metacrine, Inc., NGM Biopharmaceuticals, Novartis, Novo Nordisk, Pfizer, Prometheus, Promethera, Sanofi, Siemens, and Viking Therapeutics. In addition, his institution has received grant support from Allergan, Boehringer Ingelheim, Bristol-Myers Squibb, Cirius, Eli Lilly and Company, Galectin Therapeutics, Galmed Pharmaceuticals, GE, Genfit, Gilead, Intercept, Grail, Janssen, Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, NuSirt, Pfizer, pH Pharma, Prometheus, and Siemens. He is also the cofounder of Liponexus, Inc. The other authors have no conflicts of interest to declare.

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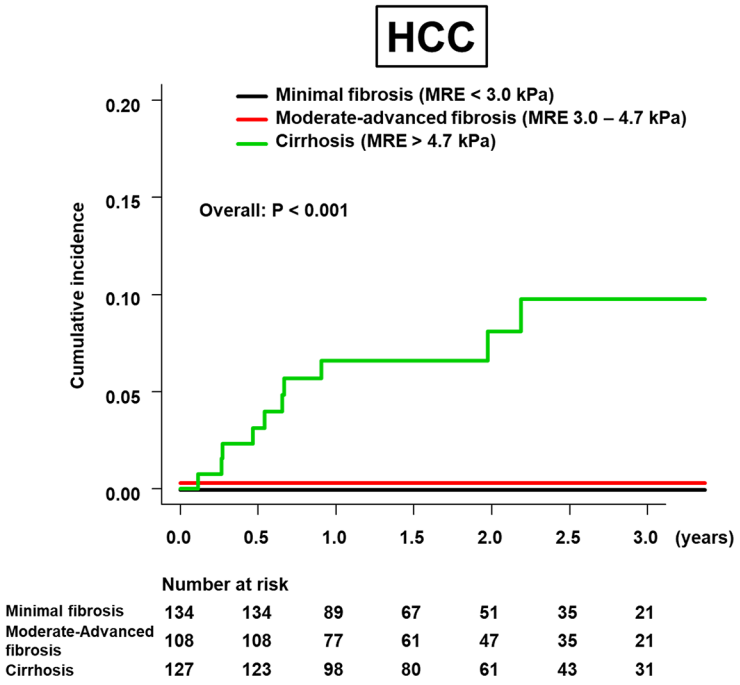

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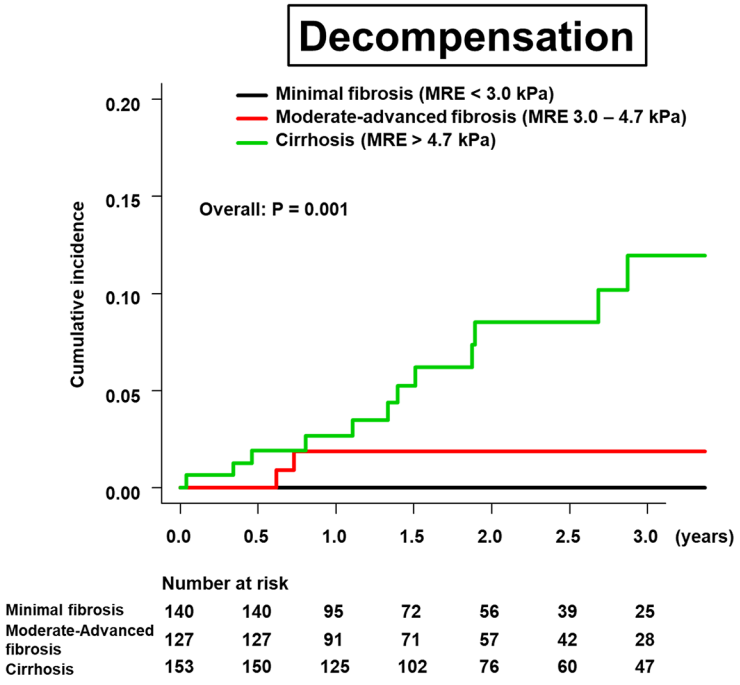

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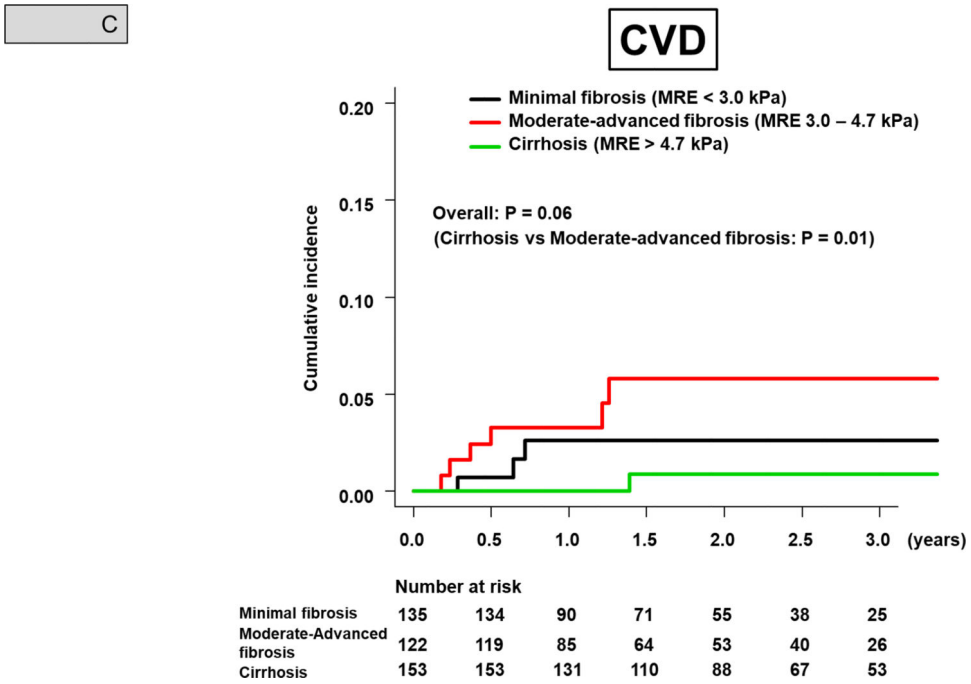

Figure 1.

The cumulative incidence of complication development

The cumulative incidence of the development of (A) HCC, (B) decompensation, and (C) CVD.

Patients were stratified into three groups according to MRE-based liver stiffness: minimal fibrosis (MRE: <3.0 kPa), moderate-advanced fibrosis (MRE: 3.0–4.7 kPa), and cirrhosis (MRE: >4.7 kPa).

HCC, hepatocellular carcinoma; CVD, cardiovascular disease; MRE, magnetic resonance elastography