Association between Atrial Fibrillation and Advanced Liver Fibrosis in Patients with Non-Alcoholic Fatty Liver Disease

Min Kyu Kang, Jung Gil Park, and Min Cheol Kim
Division of Gastroenterology and Hepatology, Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, Korea.

**Purpose:** Non-alcoholic fatty liver disease (NAFLD) is independently associated with the development of atrial fibrillation (AF). However, the association of AF with advanced liver fibrosis, which is related to all-cause, cardiovascular, and liver-related mortality, has not been established in NAFLD patients. We aimed to investigate the association between AF and advanced liver fibrosis in NAFLD patients.

**Materials and Methods:** Out of 53704 adults who participated in the health check-up program, 6293 subjects aged 35 years and older were diagnosed as NAFLD using ultrasound. The stage of liver fibrosis was assessed based on the newly adjusted NAFLD fibrosis score (NFS) and Fibrosis-4 (Fib-4) Index, which were used to determine the low and high cut-off values (COVs).

**Results:** Of 6293 patients with NAFLD, 59 (0.9%) were diagnosed with AF. Patients with AF were older (52.0 vs. 64.6 years, \( p < 0.001 \)), had higher body mass index (25.2 vs. 26.6 kg/m², \( p < 0.001 \)), and had bigger waist circumference (84.0 vs. 89.9 cm, \( p < 0.001 \)) than those without AF. In NAFLD patients, AF was independently associated with advanced liver fibrosis, assessed using both COVs of NFS [low-COV group: final adjusted odds ratios (aORs)=2.85, \( p = 0.004 \); high-COV group: ORs=12.29, \( p < 0.001 \)]. AF was independently associated with advanced liver fibrosis, assessed using both COVs of Fib-4 (low-COV group: aORs=2.49, \( p < 0.001 \); high-COV group: aORs=3.84, \( p = 0.016 \)).

**Conclusion:** AF is independently associated with advanced liver fibrosis in patients with NAFLD.

**Key Words:** Atrial fibrillation, fibrosis, metabolic syndrome, non-alcoholic fatty liver disease

**INTRODUCTION**

Non-alcoholic fatty liver disease (NAFLD) is characterized by more than 5% of hepatic steatosis in the absence of secondary cause and excessive alcohol consumption.\(^1\)\(^-\)\(^3\) The prevalence of NAFLD in South Korea is 16–33%, which is expected to increase in the future due to increasing age, obesity, and metabolic syndrome.\(^1\)\(^3\)

NAFLD has a wide variety of disease spectrum, ranging from simple steatosis, steatohepatitis, significant and advanced fibrosis, cirrhosis, liver failure, and hepatocellular carcinoma.\(^4\)

In patients with NAFLD, the presence of fibrosis as a prognostic factor is significantly associated with mortality.\(^2\) In particular, advanced fibrosis and cirrhosis are associated with liver-related and cardiovascular mortality, of which cardiovascular death is the most important cause of death in patients with NAFLD.\(^5\)\(^-\)\(^7\)

Atrial fibrillation (AF), as one of the most common aging-related cardiac arrhythmia, is associated with morbidity and mortality.\(^8\) AF characterized by irregular atrial activation, causes chronic hemodynamic variability and remodelling of the heart structure, increasing the risk of embolic stroke, heart failure, and myocardial infarction.\(^9\)\(^-\)\(^11\) In recent studies, the association between AF and NAFLD has been explored, which revealed the mechanisms associated with similar risk factors such as...
obesity, diabetes, hypertension, and hyperthyroidism.\textsuperscript{12-14}

However, the association of AF with advanced liver fibrosis, which is directly related to mortality in NAFLD patients, has not been identified. We aimed to investigate the relationship between AF and advanced liver fibrosis calculated using two non-invasive scoring systems in patients with ultrasound (US)-screened NAFLD.

**MATERIALS AND METHODS**

**Patients**

This retrospective, cross-sectional, single-institution study assessed the association between AF and advanced liver fibrosis in patients with NAFLD. From January 2010 to December 2017, 53704 adults who underwent comprehensive health screening at the Health Promotion Centre were identified. Considering that diagnostic accuracy for advanced fibrosis using NAFLD fibrosis score (NFS) and Fibrosis-4 (Fib-4) score was low in patients aged under 35 years, we excluded these patients.\textsuperscript{15}

A total of 53704 patients 1) aged <35 years (n=8361), 2) who tested positive results for hepatitis B and C (n=564 and 21, respectively), 3) with excessive alcohol consumption (male >140 g/week and female >70 g/week) (n=628),\textsuperscript{16} 4) with inadequate and missing data (n=853), 5) with no evidence of fatty liver on abdominal US (n=36984) were excluded (Fig. 1). Meanwhile, 6293 NAFLD patients were included in the final analysis. The study protocol was approved by the Institutional Review Board of Yeungnam University Hospital (IRB No. 2019-04-010).

**Measurement of clinical and laboratory data**

Weight, height, seated blood pressure (BP), and waist circumference (WC) were measured by trained nurses. The results of blood samples and abdominal US were obtained from each patient after a 12-hour overnight fasting. The patients' platelet count, fasting plasma glucose (FPG), serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), \(\gamma\)-glutamyl transferase (GGT), albumin, blood urea nitrogen, creatinine, high-sensitivity C-reactive protein (hsCRP), and lipid profiles, including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG), were measured.

Using the Asian-Pacific region criteria, obesity was defined as a body mass index (BMI) of \(\geq 25\) kg/m\(^2\).\textsuperscript{17} Based on the American Diabetes Association criteria, diabetes mellitus (DM) was defined as an FPG of \(\geq 126\) mg/dL and treatment with antidiabetic medication. In addition, impaired fasting glucose was defined as an FPG of 100–125 mg/dL.\textsuperscript{18} Hypertension was defined as 1) systolic BP of \(\geq 140\) mm Hg or 2) diastolic BP of \(\geq 90\) mm Hg or 3) taking any antihypertensive medication. Adopting the International Diabetes Federation criteria, metabolic syndrome in Asian adults was assessed based on visceral obesity (WC \(\geq 20\) cm in men and \(\geq 85\) cm in women) plus two of the following four factors: elevated TG (\(\geq 150\) mg/dL), decreased HDL-C (\(\leq 40\) mg/dL in male and \(\leq 50\) mg/dL in female), elevated BP (systolic BP \(\geq 130\) mm Hg or diastolic BP \(\geq 85\) mm Hg), and elevated FPG (\(\leq 100\) mg/dL).\textsuperscript{19}

**Assessment of AF**

A standard 12-lead electrocardiogram (ECG) using a GE MAC 5000 ECG Machine (GE Health Care, Chicago, IL, USA) was utilized to identify abnormal ECG findings, including AF. The diagnosis of AF was confirmed by experienced cardiologists who were blinded to the patients' clinical manifestations.

**Definition of fatty liver and advanced liver fibrosis using non-invasive methods**

Fatty liver was determined by two radiologists with 10 years of experience based on the following criteria: 1) increased echogenicity of the liver parenchyma brighter than that of the cortex of the kidney, 2) deep beam attenuation, and 3) blurring of the intrahepatic vessels, using EPIQ 5 and EPIQ 7 (Philips, Amsterdam, Netherlands).\textsuperscript{20} Adopting the Asia-Pacific Working Party on Non-alcoholic Fatty Liver Disease guidelines, NAFLD was diagnosed as fatty liver via careful consideration of the inclusion and exclusion criteria.\textsuperscript{16}

Advanced fibrosis in NAFLD patients was identified using non-invasive scoring systems based on clinical laboratory tests: NFS and Fib-4 index (Supplementary Table 1, only online). The NFS and Fib-4 have dual cut-off values (COVs) were obtained to determine the risk of advanced fibrosis, which was classified as low, intermediate, and high risk for advanced liver fibrosis according to NAFLD guideline of European Associ-
ation for the Study of the Liver. Low COVs of -1.455 for NFS and 1.30 for Fib-4 were a strong negative predictive value of advanced fibrosis, while high COVs of 0.676 for NFS and 2.67 for Fib-4 for were a definite positive predictive value advanced fibrosis in patients with NAFLD. In addition, new low COVs were adjusted in patients aged 65 years and above with NFS and Fib-4 indices of 0.12 and 2.0, respectively.

Statistical analysis
All statistical analyses were performed using IBM SPSS version 25.0 (IBM Corp., Armonk, NY, USA). The continuous variables are expressed as mean±standard deviation or number (%). Differences in variables between the AF and non-AF groups in patients with NAFLD were calculated using the Student’s t-test. The association between prevalence of AF and three fibrosis stages using NFS and Fib-4 was identified using linear-by-linear association test and chi-square test, respectively. The association between AF and advanced fibrosis was identified using logistic regression analysis.

With the exception of the variables included in the non-invasive scoring systems for advanced fibrosis, several adjusted models with confounding variables were tested by multivariate regression analysis. A p-value <0.05 was considered significant.

RESULTS
Baseline characteristics
The baseline characteristics stratified by the presence of AF are summarized in Table 1. Of the 6293 patients with NAFLD, 59 (0.9%) were diagnosed with AF. Compared to patients without AF (non-AF group), those with AF (AF group) were older (64.6±8.7 vs. 52.0±9.3, p<0.001), more likely to be male (79.7 vs. 58.0%, p=0.004), had higher BMI (26.6±2.8 vs. 25.2±2.6 kg/m², p<0.001), had bigger WC (89.9±7.2 vs. 84.0±7.3 cm, p<0.001), had a higher prevalence of obesity (64.4 vs. 48.3%, p=0.020), and were more likely to have DM (22.0 vs. 9.4%, p=0.002). Moreover, platelet counts, serum albumin, and FPG were significantly higher in the AF group than in the non-AF group.

The NFS and Fib-4 in the AF group were higher than those in the non-AF group (-0.9±1.0 vs. -2.3±1.1 by NFS; 1.7±0.6 vs. 1.1±0.5 by Fib-4, p<0.001, respectively) (Table 1, Fig. 2). In terms of advanced liver fibrosis with high COVs of NFS and Fib-4 score, the AF group had a greater prevalence of advanced fibrosis compared to the non-AF group (6.8% vs. 0.5% by NFS; 6.8% vs. 1.2% by Fib-4, p=0.001, respectively) (Table 1).

Prevalence of AF according to the risk of advanced liver fibrosis
Using NFS, the prevalence rates of AF were 0.4%, 2.4%, and 11.4% in the low, intermediate, and high risk for advanced liver fibrosis, respectively (p<0.001 from linear-by-linear association test). Patients with high risk for advanced liver fibrosis using

| Table 1. Baseline Characteristics |
|----------------------------------|
| **Variable**                      | **AF** | **Non-AF** | **p** |
| **Age (yr)**                      | 64.6±8.7 | 52.0±9.3 | <0.001 |
| **Male**                          | 47 (79.7%) | 3616 (58.0%) | 0.004 |
| **Body mass index (kg/m²)**       | 26.6±2.8 | 25.2±2.6 | <0.001 |
| **Waist circumference (cm)**      | 89.9±7.2 | 84.0±7.3 | <0.001 |
| **Comorbidities**                 |        |           |      |
| **Obesity**                       | 38 (64.4%) | 3011 (48.3%) | 0.020 |
| **Diabetes mellitus**             | 13 (22.0%) | 583 (8.4%) | 0.002 |
| **Hypertension**                  | 15 (25.4%) | 1027 (16.5%) | 0.096 |
| **Metabolic syndrome**            | 12 (20.3%) | 1161 (18.6%) | 0.866 |
| **Liver function tests**          |        |           |      |
| **Aspartate aminotransferase (IU/L)** | 27.5±9.4 | 26.9±12.3 | 0.669 |
| **Alanine aminotransferase (IU/L)** | 30.8±18.1 | 31.2±20.4 | 0.882 |
| **Platelet count (K/µL)**         | 212.4±48.0 | 249.2±58.0 | <0.001 |
| **Gamma-glutamyl transferase (IU/L)** | 41.3±33.5 | 35.9±37.2 | 0.266 |
| **Albumin (g/dL)**                | 4.5±0.4 | 4.7±0.6 | <0.001 |
| **Metabolic profiles (mg/dL)**    |        |           |      |
| **Fasting plasma glucose**        | 112.5±32.8 | 101.6±24.4 | 0.013 |
| **Total cholesterol**             | 193.4±47.8 | 208.4±39.2 | 0.154 |
| **Triglyceride**                  | 152.1±96.7 | 150.6±91.4 | 0.901 |
| **High-density lipoprotein**      | 49.9±11.6 | 53.8±13.5 | 0.128 |
| **Low-density lipoprotein**       | 119.1±46.4 | 124.5±36.9 | 0.374 |
| **hsCRP**                         | 0.19±0.26 | 0.13±0.29 | 0.068 |
| **Fibrosis scoring system**       |        |           |      |
| **NAFLD fibrosis score**          | -0.9±1.0 | -2.3±1.1 | <0.001 |
| **Fibrosis-4 score**              | 1.7±0.6 | 1.1±0.5 | <0.001 |
| **High probability for advanced fibrosis** | 4 (6.8%) | 31 (0.5%) | <0.001 |
| **Fibrosis-4 score**              | 4 (6.8%) | 75 (1.2%) | 0.001 |

AF, atrial fibrillation; hsCRP, high-sensitivity C reactive protein; NAFLD, non-alcoholic fatty liver disease.
Values are presented as mean±standard deviation or number (%), unless otherwise specified. High probability for advanced liver fibrosis is defined based on high cut-off value levels, which are 0.876 for NAFLD fibrosis score and 2.67 for Fibrosis-4 score.

NAFLD showed a significant higher AF prevalence than those with low and intermediate risk for advanced liver fibrosis (all p-values<0.001). In addition, patients with intermediate risk for advanced liver fibrosis showed a significantly higher AF prevalence compared to those with low risk for advanced liver fibrosis (p<0.001) (Fig. 3).

Using the Fib-4 index, the prevalence rates of AF were 0.4%, 2.2%, and 5.1% in the low, intermediate, and high risk for advanced liver fibrosis, respectively (p<0.001, from linear-by-linear association test). Patients with high probability for advanced liver fibrosis using the Fib-4 index showed a significantly higher AF prevalence compared to those with low and intermediate risk for advanced liver fibrosis, respectively (all p-values <0.001). In addition, patients with intermediate risk for advanced liver fibrosis showed a significant higher AF preva-
Univariate analysis for AF in patients with NAFLD

Table 2 shows AF-associated factors of patients with NAFLD. On univariate analysis, age (odds ratio (OR), 1.13; 95% confidence interval (CI), 1.10–1.16; p<0.001), female gender (OR, 2.86; 95% CI, 1.56–5.56, p=0.001), greater BMI (OR, 1.17; 95% CI, 1.08–1.26, p<0.001), DM (OR, 2.74; 95% CI, 1.41–4.95, p=0.001), low platelet count (OR, 0.26; 95% CI, 0.15–0.44, p<0.001), and low HDL-C (OR, 0.98; 95% CI, 0.96–1.00, p=0.028) were associated with AF. In addition, greater NFS (OR, 2.82; 95% CI, 2.26–3.53, p<0.001) and Fib-4 score (OR, 1.84; 95% CI, 1.46–2.41, p<0.001) were associated with AF, respectively.

Next, we investigated the association between AF and advanced fibrosis using two fibrosis scoring systems by multivariate analysis. However, considering that the formulas of NFS and FIB-4 consist of various variables, we evaluated the association between AF and advanced fibrosis by sequentially applying other variables that are not included in the formula. Using dual COVs of two fibrosis scoring systems, we also investigated the association between AF and advanced fibrosis according to the inclusion and exclusion of intermediate risk.

Association between AF and advanced liver fibrosis classified by dual COVs of the NAFLD fibrosis score

As shown in Table 3, the association between AF and advanced fibrosis, using dual NFS COVs, remained statistically significant by sequential adjusted models. The variables applied to NFS formulas were excluded in the adjusted models. Using low NFS COVs, the strength of associations between
AF and advanced liver fibrosis in NAFLD patients was not attenuated after the adjustment for gender, hypertension, and obesity (model 1: OR, 3.20; 95% CI, 1.90–5.37, p<0.001); after further adjustment for FPG, GGT, and hsCRP (model 2: OR, 2.85; 95% CI, 1.66–4.84, p=0.001); and after adjustment for lipid profiles, including TC, TG, HDL-C, and LDL-C (model 3: OR, 2.85; 95% CI, 1.66–4.84, p=0.004). The association between AF and advanced fibrosis was not maintained after sequential adjustment based on model 1 (OR, 5.53; 95% CI, 1.93–15.85; p=0.001), model 2 (OR, 5.53; 95% CI, 1.93–15.85; p=0.001), and model 3 (OR, 3.84; 95% CI, 1.29–11.43; p=0.016) (Table 4).

**DISCUSSION**

In this study, we evaluated the association between AF and advanced liver fibrosis using dual COVs in patients with NAFLD. Regardless of the application of two dual COVs in two different representative non-invasive formulas, the relationship between AF and advanced fibrosis was not attenuated after further adjustments. Namely, AF is associated with advanced liver fibrosis in patients with NAFLD, independently of metabolic risk factors.

In previous studies, the putative association between AF and NAFLD was established. A positive correlation was observed between circulating liver enzymes, including transaminase and GGT, as a possible marker of NAFLD and the incidence of AF. In patients with type 2 DM, Targher et al. demonstrated that the incidence and prevalence of persistent/permanent AF in NAFLD patients were higher than those in non-NAFLD patients. Although NAFLD and AF share the same risk factors and comorbid conditions, their pathophysiological mechanisms have not been completely understood.

In patients with NAFLD, which is associated with insulin re-
sistance (IR) and visceral obesity, the accumulated adipose tissue is degraded by the activation of inflammatory cytokines associated with sustained IR.2,4,5 Chronic inflammation is maintained due to increased free fatty acid and release of inflammatory cytokine, including nuclear factors-kB and interleukin-6.26-28 The persistence of chronic inflammation leads to enhanced oxidative stress, destruction of gradual mitochondrial, and the production of pro-inflammatory factors and pro-thrombogenic molecules, which in turn are associated with hepatic histologic progression as well as myocardial stress and structural derangements, leading to advanced liver fibrosis and thus AF.26,27,29 Therefore, we presume that advanced liver fibrosis and cardiac remodelling followed by chronic inflammation caused the AF in NAFLD patients, which suggests putative mechanism between the two diseases. In addition, NAFLD is an independent risk factor for autonomic dysfunction, which is related to the variability of sympathovagal balance and initiation of profibrillatory and prothrombotic pathway with structural remodelling.30,31 Therefore, cardiac autonomic dysfunction and structural remodelling due to long-term exposure to systemic pathogenic mediators are putative mechanisms leading to the persistence and exacerbation of AF in NAFLD patients with advanced liver fibrosis.

For assessment of fibrosis in patients with NAFLD, liver biopsy is currently the gold standard for diagnosis.35 However, liver biopsy has the following limitations: invasiveness including fatal complications, sampling bias, and inter- and intra-observer variability.36 For these reasons, two non-invasive scoring systems using clinical and biochemical variables have been proposed to predict advanced liver fibrosis in patients with NAFLD. For NAFLD patients aged over 35 years, the two COVs were defined according to the two scoring systems. In terms of NFS, a score of <1.455 has a 93% negative predictive value for predicting the presence of advanced fibrosis, whereas a score of >0.676 has a 90% positive predictive value for predicting the presence of advanced fibrosis.4 In terms of Fib-4, a score of <1.30 has a 93% negative predictive value for predicting the presence of advanced fibrosis, whereas a score of >2.67 has an 80% positive predictive value for predicting the presence of advanced fibrosis. In our study, as the risk of advanced fibrosis increased, the prevalence of AF significantly increased. After the adjustment of traditional metabolic risk factors and comorbidity, the association between AF and advanced liver fibrosis was not attenuated by dual COVs of both scoring models in patients with NAFLD. In particular, the association between AF and advanced liver fibrosis stratified with low COV remains significant. Although patients with advanced liver fibrosis with low COV were stratified in the intermediate group, the association between these two is still statistically significant.

This study had some limitations. First, due to the cross-sectional, retrospective nature of this single-centre study, it is difficult to determine any causal relationship between AF and advanced liver fibrosis and to generalise the results to the general population with NAFLD. Due to the characteristics of AF and advanced liver fibrosis associated with aging, a long-term cohort study including the duration of the two diseases is required. In our study, the median age of the AF group with NAFLD was 66 years with a prevalence of 0.9%, which was lower than that (2.28%) reported in previous studies conducted in Koreans aged over 60 years.37 In other words, the sample used in our study cannot represent the general population due to the potential for selection bias in examinees who are concerned about health and able to afford medical expense.

Second, US was used to diagnose fatty liver, which has inter- and intra-observer subjective interpretation as well as inaccurate detection in patients with mild steatosis (<33%).20 Third, the diagnosis of AF was based only on the results of the 12-lead ECG, which has a limitation for diagnosing paroxysmal AF.

Finally, due to the inability of the homeostasis model assessment (HOMA) to measure IR levels in our health promotion centre, the association between IR and AF was not clearly elucidated. In another study, no significant relationship was observed between IR using HOMA and incident AF.34 Therefore, future studies should identify the association between IR and AF.

In conclusion, AF is independently associated with advanced liver fibrosis in patients with NAFLD, regardless of traditional metabolic factors. Considering that the occurrence of AF increases from intermediate risk for advanced fibrosis, strategy for screening of AF would be considered in NAFLD patients with intermediate or high risk for advanced liver fibrosis.

ACKNOWLEDGEMENTS

This research was supported by the Basic Science Research Program and Bio & Medical Technology Development Program through the National Research Foundation of Korea (NRF), funded by the Ministry of Science, ICT and Future Planning [2017R1C1B5076851], and the Korean government [2019M3E5D1A02068089].

AUTHOR CONTRIBUTIONS

Conceptualization: Min Kyu Kang and Jung Gil Park. Data curation: Min Kyu Kang and Min Cheol Kim. Formal analysis: Min Kyu Kang and Min Cheol Kim. Funding acquisition: Min Kyu Kang and Jung Gil Park. Investigation: Min Cheol Kim. Methodology: Min Kyu Kang. Project administration: Jung Gil Park and Min Cheol Kim. Resources: Min Kyu Kang. Software: Min Cheol Kim. Supervision: Jung Gil Park. Visualization: Min Cheol Kim. Writing—original draft: Min Kyu Kang and Min Cheol Kim. Writing—review & editing: Jung Gil Park and Min Cheol Kim. Approval of final manuscript: all authors.

ORCID iDs

Min Kyu Kang https://orcid.org/0000-0002-1435-3312
Jung Gil Park https://orcid.org/0000-0001-5472-4731
AF and Advanced Liver Fibrosis in NAFLD Patients

Min Cheol Kim https://orcid.org/0000-0002-2234-8070

REFERENCES

1. Lee YH, Bang H, Park YM, Bae JC, Lee BW, Kang ES, et al. Non-laboratory-based self-assessment screening score for non-alcoholic fatty liver disease: development, validation and comparison with other scores. PLoS One 2014;9:e107584.

2. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther 2011;34:274-85.

3. Yoo JJ, Kim W, Kim MY, Jun DW, Kim SG, Yeon JE, et al. Recent research trends and updates on nonalcoholic fatty liver disease. Clin Mol Hepatol 2019;25:1-11.

4. Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology 2007;45:846-54.

5. Angulo P, Klein DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya P, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology 2015;149:389-97.e10.

6. Ekstedt M, Hagström H, Nasr P, Fredrikson M, Stål P, Kechagias S, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology 2015;61:1547-54.

7. Henson JB, Simon TG, Kaplan A, Osganian S, Masia R, Corey KE. Advanced fibrosis is associated with incident cardiovascular disease in patients with non-alcoholic fatty liver disease. Aliment Pharmacol Ther 2020;51:728-36.

8. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. Circulation 2004;110:1042-6.

9. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur J Cardiothorac Surg 2016;50:e1-88.

10. Wijarnpreecha K, Boonpheng B, Thongprayoon C, Jaruvongvanich M, Rienstra M, Magnani JW, et al. Relation of circulating liver transaminase concentrations to risk of new-onset atrial fibrillation. Am J Cardiol 2013;111:219-24.

11. Alonso A, Misailek JR, Amiinu MA, Hoogeveen RC, Chen LY, Agarwal SK, et al. Circling levels of liver enzymes and incidence of atrial fibrillation: the Atherosclerosis Risk in Communities cohort. Heart 2014;100:1511-6.

12. Yoon HJ, Lee YH, Cha BS. Causal relationship of non-alcoholic fatty liver disease with obesity and insulin resistance. J Korean Diabetes 2014;15:76-81.

13. Moon JS, Yoon JS, Won KC, Lee HW. The role of skeletal muscle in development of nonalcoholic fatty liver disease. Diabetes Metab J 2013;37:278-85.

14. Mantovani A, Ballestri S, Lonardo A, Targher G. Cardiovascular disease and myocardial abnormalities in nonalcoholic fatty liver disease. Dig Dis Sci 2016;61:1246-67.

15. Kang MK, Park JG, Lee HJ, Kim MC. Association of low skeletal muscle mass with advanced liver fibrosis in patients with non-alcoholic fatty liver disease. J Gastroenterol Hepatol 2019;34:1633-40.

16. Wong VW, Chan WK, Chitturi S, Chawla Y, Dan YY, Duseja A, et al. Asia-Pacific working party on non-alcoholic fatty liver disease guidelines 2017-part 1: definition, risk factors and assessment. J Gastroenterol Hepatol 2018;33:70-85.

17. Oh SW. Obesity and metabolic syndrome in Korea. Diabetes Metab J 2011;35:561-6.

18. Peiris D, Sun L, Patel A, Tian M, Essue B, Jan S, et al. Systematic medical assessment, referral and treatment for diabetes care in China using lay family health promoters: protocol for the SMART-Diabetes cluster randomised controlled trial. Implement Sci 2016;11:116.

19. Grundy SM. Metabolic syndrome update. Trends Cardiovasc Med 2016;26:364-73.

20. Mathiesen UL, Franzén LE, Aselius H, Resjö M, Jacobsson L, Forberg U, et al. Increased liver echogenicity at ultrasound examination reflects degree of steatosis but not of fibrosis in asymptomatic patients with mild/moderate abnormalities of liver transaminases. Dig Liver Dis 2002;34:516-22.

21. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the Management of Non-Alcoholic Fatty Liver Disease. Obes Facts 2016;9:65-90.

22. Sinner MF, Wang N, Fox CS, Fontes JD, Rienstra M, Magnani JW, et al. Relation of circulating liver transaminase concentrations to risk of new-onset atrial fibrillation. Am J Cardiol 2013;111:219-24.

23. Alonso A, Misailek JR, Amiinu MA, Hoogeveen RC, Chen LY, Agarwal SK, et al. Circling levels of liver enzymes and incidence of atrial fibrillation: the Atherosclerosis Risk in Communities cohort. Heart 2014;100:1511-6.

24. Yoon HJ, Lee YH, Cha BS. Causal relationship of non-alcoholic fatty liver disease with obesity and insulin resistance. J Korean Diabetes 2014;15:76-81.

25. Moon JS, Yoon JS, Won KC, Lee HW. The role of skeletal muscle in development of nonalcoholic fatty liver disease. Diabetes Metab J 2013;37:278-85.

26. Mantovani A, Ballestri S, Lonardo A, Targher G. Cardiovascular disease and myocardial abnormalities in nonalcoholic fatty liver disease. Dig Dis Sci 2016;61:1246-67.

27. Kang MK, Park JG, Lee HJ, Kim MC. Association of low skeletal muscle mass with advanced liver fibrosis in patients with non-alcoholic fatty liver disease. J Gastroenterol Hepatol 2019;34:1633-40.

28. Ballestri S, Lonardo A, Bonapace S, Byrne CD, Loria P, Targher G. Risk of cardiovascular, cardiac and arrhythmic complications in patients with non-alcoholic fatty liver disease. World J Gastroenterol 2014;20:1724-45.

29. Kärkäjäimäki AJ, Päät P, Savolainen M, Keskilämaa Y, Ruokonen L, Rahman J, et al. Sarcopenia is associated with severe liver fibrosis in patients with non-alcoholic fatty liver disease. Aliment Pharmacol Ther 2017;45:510-8.

30. Liu YC, Hung CS, Wu YW, Lee YC, Lin YH, Lin C, et al. Inflammation of non-alcoholic fatty liver disease on autonomic changes evaluated by the time domain, frequency domain, and symbolic dynamics of heart rate variability. PLoS One 2013;8:e61803.

31. Li HW, Chiu CF, Hsu PH, Lin YH, Lin C, et al. Inflammation of non-alcoholic fatty liver disease on autonomic changes evaluated by the time domain, frequency domain, and symbolic dynamics of heart rate variability. PLoS One 2013;8:e61803.
and prevalence of atrial fibrillation and estimated thromboembolic risk using the CHA2DS2-VASc score in the entire Korean population. Int J Cardiol 2017;236:226-31.

34. Fontes JD, Lyass A, Massaro JM, Rienstra M, Dallmeier D, Schnabel RB, et al. Insulin resistance and atrial fibrillation (from the Framingham Heart Study). Am J Cardiol 2012;109:87-90.