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

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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/m^2, $p<0.001$), 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.[5] 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

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obesity, diabetes, hypertension, and hyperthyroidism.[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.[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),[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).

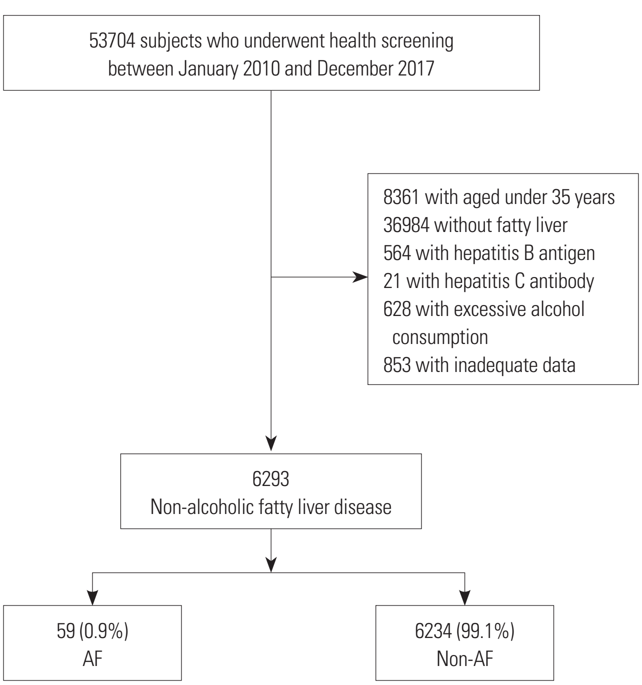

Fig. 1. Flow chart of non-alcoholic fatty liver patients according to the presence of atrial fibrillation (AF).

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), γ-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 ≥25 kg/m^2.[17] Based on the American Diabetes Association criteria, diabetes mellitus (DM) was defined as an FPG of ≥126 mg/dL and treatment with antidiabetic medication. In addition, impaired fasting glucose was defined as an FPG of 100−125 mg/dL.[18] Hypertension was defined as 1) systolic BP of ≥140 mm Hg or 2) diastolic BP of ≥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 ≥0 cm in men and ≥85 cm in women) plus two of the following four factors: elevated TG (≥150 mg/dL), decreased HDL-C (≤40 mg/dL in male and ≤50 mg/dL in female), elevated BP (systolic BP ≥130 mm Hg or diastolic BP ≥85 mm Hg), and elevated FPG (≤100 mg/dL).[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).[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.[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 Association for the Study of the Liver.[21] 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.[15]

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 years, *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/m^2, *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 n=59 (0.9%)	Non-AF n=6234 (99.1%)	*p* value
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/m^2)	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 (9.4)	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	199.4±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			
NAFLD fibrosis score	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 0.676 for NAFLD fibrosis score and 2.67 for Fibrosis-4 score.

NFS 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-

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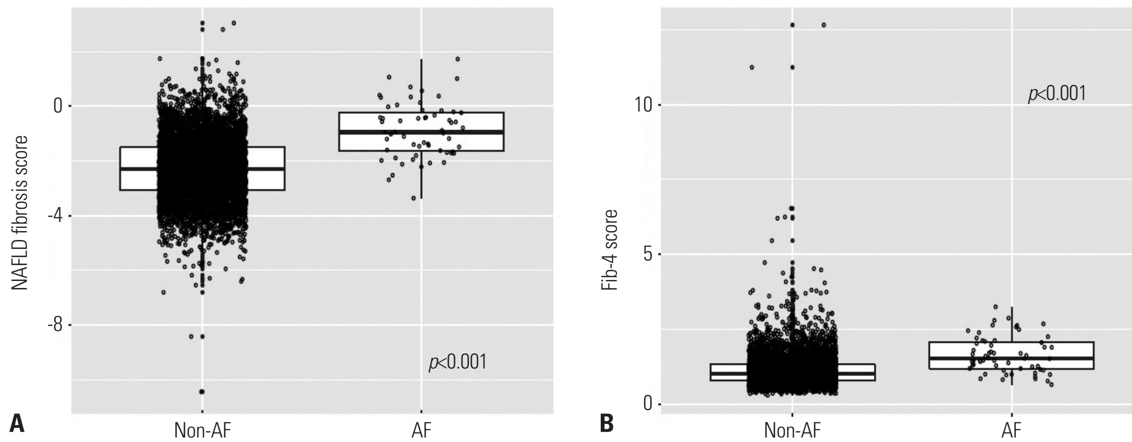

Fig. 2. Comparison of values of two non-invasive scoring systems according to the presence of atrial fibrillation (AF) in patients with non-alcoholic fatty liver disease (NAFLD). The NFS and Fib-4 in the AF group were higher than those in the non-AF group (0.9±1.0 vs. 2.3±1.1 by NFS (A); 1.7±0.6 vs. 1.1±0.5 by Fib-4 (B), p<0.001, respectively). Fib-4, fibrosis-4.

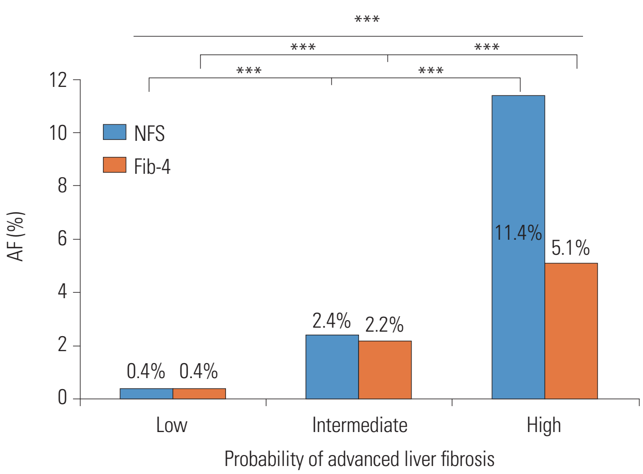

Fig. 3. Comparison of percentages of atrial fibrillation (AF) according to the grade of probability for advanced liver fibrosis defined by two non-invasive scoring systems in patients with non-alcoholic fatty liver disease (NAFLD). ***p<0.001. NFS, NAFLD fibrosis score; Fib-4, fibrosis-4.

lence compared to those with low risk for advanced liver fibrosis (p<0.001) (Fig. 3).

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.

Table 2. Univariate Analysis of Risk Factors for Atrial Fibrillation in Patients with NAFLD

Variable	OR (95% CI)	*p* value
Age (yr)	1.13 (1.10–1.16)	<0.001
Female	2.86 (1.56–5.56)	0.001
Body mass index (kg/m^2)	1.17 (1.08–1.26)	<0.001
Diabetes mellitus	2.74 (1.41–4.95)	0.001
Hypertension	1.73 (0.93–3.04)	0.069
Aspartate aminotransferase (IU/L)	1.00 (0.98–1.02)	0.741
Alanine aminotransferase (IU/L)	1.00 (0.98–1.01)	0.882
Platelet count (K/μL)	0.26 (0.15–0.44)	<0.001
Gamma-glutamyl transferase (IU/L)	1.19 (0.69–1.54)	0.334
Fasting plasma glucose (mg/dL)	2.69 (1.38–4.58)	<0.001
Total cholesterol (mg/dL)	0.99 (0.99–1.00)	0.079
Triglyceride (mg/dL)	1.02 (0.75–1.29)	0.903
High-density lipoprotein (mg/dL)	0.98 (0.96–1.00)	0.028
Low-density lipoprotein (mg/dL)	1.00 (0.99–1.00)	0.261
hsCRP (mg/dL)	1.00 (0.97–1.01)	0.144
NAFLD fibrosis score	2.82 (2.26–3.53)	<0.001
Fibrosis-4 score	1.84 (1.46–2.41)	<0.001

OR, odds ratio; CI, confidence interval; hsCRP, high sensitivity C reactive protein; NAFLD, non-alcoholic fatty liver disease.

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

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Table 3. Adjusted Odd Ratios of Advanced Liver Fibrosis Defined as the Dual COVs of Non-Alcoholic Fatty Liver Fibrosis Score for AF in Patients with Non-Alcoholic Liver Disease

	AF	
	OR (95% CI)	*p* value
Advanced fibrosis (F3–4) by low COV of NFS (yes vs. no)		
Unadjusted	3.38 (2.01–5.67)	<0.001
Gender adjusted	3.20 (1.90–5.37)	<0.001
Model 1	3.20 (1.90–5.37)	<0.001
Model 2	2.85 (1.66–4.84)	0.001
Model 3	2.85 (1.66–4.84)	0.004
Advanced fibrosis (F3–4) by high COV of NFS (yes vs. no)		
Unadjusted	14.55 (4.97–42.62)	<0.001
Gender adjusted	16.41 (5.51–48.84)	<0.001
Model 1	15.83 (5.32—47.17)	<0.001
Model 2	12.29 (3.48–33.79)	<0.001
Model 3	12.29 (3.48–33.79)	<0.001

AF, atrial fibrillation; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio; COV, cut-off value; NFS, NAFLD fibrosis score; CI, confidence interval.
NFS levels <-1.455 and >0.675 were considered to indicate the absence of advanced fibrosis and diagnosis confirmation of advanced fibrosis in patients of NAFLD, respectively. In addition, new low COVs were adjusted in patients aged 65 years and older with NFS indices of 0.12. Model 1: gender, presence of hypertension, and obesity, Model 2: further adjusted for fasting plasma glucose, gamma-glutamyl transferase, and high-sensitivity C reactive protein, Model 3: further adjusted for total cholesterol, triglyceride, high-density lipoprotein, and low-density lipoprotein.

Table 4. Adjusted Odd Ratios of Advanced Liver Fibrosis Defined as the Dual COVs of Fib-4 Index for AF in Patients with Non-Alcoholic Liver Disease

	AF	
	OR (95% CI)	*p* value
Advanced fibrosis (F3–4) by low COV of Fib-4 (yes. vs. no)		
Unadjusted	2.86 (1.71–4.80)	<0.001
Gender adjusted	2.86 (1.71–4.80)	<0.001
Model 1	2.67 (1.58–4.49)	<0.001
Model 2	2.67 (1.58–4.49)	<0.001
Model 3	2.49 (1.47–4.21)	<0.001
Advanced fibrosis (F3–4) by high COV of Fib-4 (yes. vs. no)		
Unadjusted	5.97 (2.11–16.90)	<0.001
Gender adjusted	5.88 (2.07–16.72)	<0.001
Model 1	5.53 (1.93–15.85)	0.001
Model 2	5.53 (1.93–15.85)	0.001
Model 3	3.84 (1.29–11.43)	0.016

AF, atrial fibrillation; Fib-4, fibrosis-4; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio; COV, cut-off value; NFS, NAFLD fibrosis score; CI, confidence interval.
Fib-4 index levels <1.30 and >2.67 were considered to indicate the absence of advanced fibrosis and diagnosis confirmation of advanced fibrosis in patients of NAFLD, respectively. In addition, new low COVs were adjusted in patients aged 65 years and older with FIB-4 indices of 2.0. Model 1: gender, presence of diabetes, hypertension, and obesity, Model 2: further adjusted for total cholesterol, triglyceride, and high-density lipoprotein, and low-density lipoprotein, Model 3: further adjusted for albumin, gamma-glutamyl transferase, and high-sensitivity C-reactive protein.

AF and advanced fibrosis 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 using a high COV of NFS was also maintained after sequential adjustment based on model 1 (OR, 15.83; 95% CI, 5.32–47.17, *p*<0.001), model 2 (OR, 12.29; 95% CI, 3.48–33.79, *p*<0.001), and model 3 (OR, 12.29; 95% CI, 3.48–33.79, *p*<0.001) (Table 3).

Association between the presence of AF and advanced liver fibrosis classified by dual COVs of the Fib-4 score

Table 4 shows the relationship between AF and advanced liver fibrosis, defined by dual COVs of Fib-4. The adjusted model was not stratified by age, AST, ALT, and platelet count, which are the components of Fib-4 index. Adjustment for gender, DM, hypertension, and obesity (model 1: OR, 2.67; 95% CI, 1.58–4.49; *p*<0.001), after further adjustment for lipid profiles, including TC, TG, HDL-C, and LDL-C (model 2: OR, 2.67; 95% CI, 1.58–4.49; *p*<0.001), and after additional adjustment for serum albumin, GGT, and hsCRP (model 3: OR, 2.49; 95% CI, 1.47–4.21, *p*=0.001), did not attenuate the association between AF and advanced liver fibrosis classified by low COV. The association between AF and advanced fibrosis using a high NFS COV was also 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 enzyme, including transaminase and GGT, as a possible marker of NAFLD and the incidence of AF.[22,23] In patients with type 2 DM, Targher, et al.[12,14] 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-

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sistance (IR) and visceral obesity, the accumulated adipose tissue is degradated by the activation of inflammatory cytokines associated with sustained IR.[24,25] Chronic inflammation is maintained due to increased free fatty acid and release of inflammatory cytokine, including nuclear factors-κB 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 prothromogenic 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.[32] However, liver biopsy has the following limitations: invasiveness including fatal complications, sampling bias, and inter- and intra-observer variability.[32] 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.[33] 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.

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