Higher fatty liver index is associated with increased risk of new onset heart failure in healthy adults: A nationwide population-based study in Korea

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Abstract

Background Heart failure (HF) is relatively common cardiovascular disease with high mortality and morbidity. Although it is associated with many cardiovascular risk factors, the association between nonalcoholic fatty liver disease (NAFLD), the most common chronic liver disease, and HF has not been evaluated in a large-scale cohort study. Thus, we evaluated the ability of the fatty liver Index (FLI), a surrogate marker of NAFLD, to predict the development of HF in healthy individuals. **Methods** We evaluated 308,578 healthy persons without comorbidities who underwent the National Health check-ups in the republic of Korea from 2009 to 2014. The association between the FLI and HF was analyzed using multivariate Cox proportional-hazards models. **Results** During a median of 5.4 years' follow-up, 2,532 subjects (0.8%) were newly diagnosed with HF. Subjects were categorized into quartile groups according to FLI (Q1, 0-4.9; Q2, 5.0-12.5; Q3, 12.6-31.0; and Q4, >31.0). The cumulative incidence of HF was significantly higher in subjects with the highest FLI than in those with the lowest FLI (Q1, 307 [0.4%] and Q4, 890 [1.2%]; $P<0.001$). Adjusted hazard ratios (HRs) indicated that the highest FLI was independently associated with an increased risk for HF (HR between Q4 and Q1, 2.709; 95% confidence interval=2.380-3.085; $P<0.001$). FLI was significantly associated with increased risk of new-onset HF regardless of their baseline characteristics. **Conclusions** Higher FLI was independently associated with increased risk of HF in healthy Korean population.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common form of chronic liver disease. Its estimated prevalence is about 15-30% in general population [1]. The prevalence of NAFLD has been increasing along with the increase of obesity, insulin resistance and non-insulin dependent diabetes mellitus, and metabolic syndrome [2]. NAFLD can be found in about 60-70% among obese or diabetic population [1]. There are many studies showing associations between NAFLD and established cardiovascular risk factors including abdominal obesity, dyslipidemia, insulin resistance and high blood pressure [3]. These cardiovascular risk factors are also components of metabolic syndrome. Thus, NAFLD is regarded as the hepatic manifestation of metabolic syndrome. Moreover, cardiovascular disease is the most common cause of death in patients with NAFLD, besides extrahepatic malignancies and liver-related complications [4, 5].

Heart failure (HF) is one of major cardiovascular diseases with higher morbidity, mortality, and healthcare costs around the world [6, 7]. The prevalence of HF is approximately 1–2% of the adult population in developed countries and its prevalence is rising among aged people ($\geq 10\%$ among people >70 years of age) [6, 8]. HF and NAFLD often coexist because they share the same risk factors and a similar pathophysiological processes [9, 10]. HF may cause liver disease, and liver disease may leads to HF in the absence of other cardiovascular risk factors [10].

Although there are several studies with small sample size showing the co-existence of HF and NAFLD [11, 12], they showed the simple association in several cross-sectional studies. We analyzed a large cohort consisting of a healthy Korean adult population without known traditional cardiovascular risk factors and co-morbidities to identify the association of NAFLD and new onset HF.

Methods

Data sources

We analyzed National Health Insurance Service-National Sample Cohort 2.0 (NHIS-NSC 2.0) data set. The Korean government has an obligatory public health insurance program, National Insurance Health Service (NIHS), including more than 97% of Korean people are affiliated. Total population ($n=48,222,537$) were classified into 2,142 classes according to their age, sex, area, eligibility status, and income level. Then, Korean government randomly selected 2.1% of them from each stratum ($n=1,021,208$) from 2006 and made NHIS-NSC 2.0. It also included retrospective and

prospective follow-up data which was collected from 2002 to 2015.[13] Because the NHIS covers about 97% of the total population of Korea, the NHIS-NSC 2.0 cohort is expected to represent the entire Korean population.

The cohort includes 4 datasets: the dataset of the sociodemographic information; the dataset of medical claims including information on the diagnosis based on the 10th revision of the International Classification of Disease (ICD-10) codes, admission, and treatment; the dataset of the National Health Screening of the cohort members; and the dataset of the medical institutions. The Korean government recommends the entire Korean adults to take the National Health check-up biennially including questionnaires on medical history and health-related behaviors including smoking status and alcohol consumption, chest X-ray, physical examinations and blood tests. About 72.1% of eligible population had National Health screening programs according to the 2013 NHIS statistics [13]. The cohort also includes mortality data from the death registration database of the Statistics Korea, a central government organization for statistics.

The NHIS-NSC 2.0 is open to any researchers if the NHIS review committee approves study protocol. This study was approved by the Institutional Review Board of the Chungnam National University Hospital, Daejeon, Korea (IRB No. 2019-10-053). Our IRB waived the requirement for informed consent.

Study population

We included population over 20 years of age having National Health check-ups at least one time from 2009 to 2014. We regarded the data from the first check-up as the index data, and the year of the index check-up as the index year. We included all subjects with age $\geq$ 20 years old and excluded all subjects having pre-specified exclusion criteria; 1) those who diagnosed with comorbid conditions including congestive heart failure, hypertension, diabetes, atrial fibrillation, cerebrovascular disease, ischemic heart disease, peripheral vascular disease, valvular heart disease, liver disease, chronic pulmonary disease, chronic kidney disease, and autoimmune disease before the index year, 2) those who were prescribed with medications including oral hypoglycemic, antihypertensive, or lipid-lowering agents within 1 year before the index check-up, 3) those who answered questionnaires to have comorbid conditions at the index check-up, 4) those who with increased baseline systolic blood pressure (SBP) $\geq$ 140mmHg or diastolic blood pressure (DBP) $\geq$ 90mmHg, and fasting blood glucose $\geq$ 126mg/dL at the index check-up, and 5) those who with missing data in the index check-up.

Definition of HF

. The primary outcome of this study was HF incidence according to FLI, and the incidence of HF was defined as the first occurrence during at least 2 different days of hospital visits, at HF admission, or death with a diagnosis of HF. We assessed each diagnosis based on the data from questionnaires, and the 1-year claim data before the index year. When we used the claims data, we defined each diagnosis as the first occurrence during at least two different days of hospital visits (outpatient) or on the first admission, as likely a diagnosis of HF. The presence of HF was defined as those with "HF" according to the ICD-10 disease code in the claim dataset. HF patients who were assigned the following ICD-10 disease codes were considered as: "hypertensive heart disease with HF" (I10.0), "hypertensive heart disease with hypertensive kidney disease with HF" (I13.0), "hypertensive heart disease with hypertensive kidney disease with HF and kidney failure" (I13.2), "ischemic cardiomyopathy" (I25.5), "dilated cardiomyopathy" (I42.0), "cardiomyopathy, unspecified" (I42.9), "cardiomyopathy in diseases classified elsewhere" (I43), "HF" (I50) including "congestive HF" (I50.0), "left ventricular failure" (I50.1), and "HF, unspecified" (I50.9).

Definition of data

We calculated body mass index (BMI) with dividing weight (kg) by height (m)-squared. Population with a BMI of ≥ 25 kg/m² was regarded as obesity according to the World Health Organization guideline for the Asian population.[14] Smoking status was classified into 3 categories: non-smoker, ex-smoker, and current smoker. Alcohol consumption was evaluated with using standardized self-reporting questionnaires. The questionnaires about alcohol consumption were composed of the questions asking the number of days a week alcohol is consumed, and the amount of alcohol consumed on each drinking day. The amount of alcohol consumption was calculated by multiplying them. The questionnaires about physical activity were composed of the questions asking the number of days a week 30 minutes of light exercise, 30 minutes of moderate exercise, and 20 minutes of vigorous exercise are performed, respectively. Light exercise was assumed to be 2 METs, moderate 3 METs, and vigorous 6 METs, which were multiplied by 20, 30, and 30 minutes and the respective number of days a week, and summed.

Considering the nation-wide scale of this study, laboratory test cannot be performed in a central facility. Instead, blood samples were analyzed in a number of different institutions which were qualified by an external quality assessment service, annually conducted by Korean Association of External Quality Assessment Service. Data were censored at the time of HF occurrence, disqualification of the NHIS (death or immigration), or the end of the study (December 31th, 2015).

Calculation fatty liver index

We used a well validated, surrogate marker, FLI to identify patients with NAFLD [13]. FLI was calculated with 4 variables (triglycerides [TG], BMI, gamma-glutamyl transferase [GGT], and waist circumference [WC]) with following equation:

$$FLI = (e^{0.953 \cdot \log_e(TG) + 0.139 \cdot BMI + 0.718 \cdot \log_e(GGT) + 0.053 \cdot WC - 15.745}) / (1 + e^{0.953 \cdot \log_e(TG) + 0.139 \cdot BMI + 0.718 \cdot \log_e(GGT) + 0.053 \cdot WC - 15.745}) \cdot 100$$

The original study showed that the FLI more than 60 as the cutoff for the diagnosis of fatty liver with positive likelihood ratio of 4.3 in general population.[15] Although the FLI is simple to calculate, and easy to screen fatty liver disease, there has been insufficient evidence regarding the diagnosis of fatty liver disease with FLI in Asians because of lower BMI and WC than other ethnic population [16]. Thus, we categorized our study group into quartiles according to their FLI and used quartile group in the statistical analysis.

Statistical analysis

We used continuous variables as mean $\pm$ standard deviation and categorical parameters as number with percentage. We performed all statistical analysis with using R software version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org). Chi-square test and one-way analysis of variance test were used to evaluate statistical differences among the FLI quartiles. The calculation of cumulative event rates according to the FLI quartiles was done with Kaplan-Meier method and compared with a log-rank test. Adjusted hazard ratios (HR) and 95% confidence interval (CI) for HF incidence were estimated with Cox proportional hazard regression analysis. In the multivariate analysis, we adjusted age and sex in the model 1, and clinical characteristics associated with new onset HF of borderline statistical significance ($P < 0.100$) along with age and sex in the model 2. We excluded several confounding factors such as hypertension and diabetes because they have significant associations with NAFLD. The inclusion of NAFLD along with

these risk factors in the multivariate model might have introduced multicollinearity into the model. P values of < 0.05 were considered statistically significant.

Results

Baseline characteristics of the participants

We analyzed 308,578 subjects after the exclusion of 248,306 subjects who having the pre-specified exclusion criteria. The number of the subjects matching each exclusion criteria was presented in the Figure 1. We divided our study population into 4 groups according to their FLI quartile values; first quartile (Q1), 0 - 4.9; second quartile (Q2), 5.0 – 12.5; third quartile (Q3), 12.6 – 31.0; and fourth quartile (Q4), >31.0. The comparison of baseline clinical characteristics and laboratory findings according to the FLI quartiles was summarized in the table 1. The subjects with higher FLI had a trend to higher age and higher incidence of male. BMI, waist circumference, blood pressures, the amount of alcohol consumption and the proportion of current smoker tended to increase from Q1 to Q4. Fasting glucose, total cholesterol, triglyceride and LDL cholesterol levels were increasing along with the increase of FLI quartiles.

Association between FLI and the incidence of HF

The total follow-up duration of this study cohort was median 5.4 years (interquartile range, 4.1 - 6.3), 2,532 subjects (0.8%) had new onset HF. Table 2 shows the result of univariate analysis of new onset HF. Male gender, older age, higher BMI, higher total cholesterol, TG, and lower HDL cholesterol were associate significantly with new onset HF. Cumulative incidences of new onset HF according to the FLI quartiles were presented in the figure 2. The incidence of HF was significantly higher in the subjects with higher FLIs, compared to those with lower FLIs (Q1, 307 [0.4%]; Q2, 543 [0.7%]; Q3, 792 [1.0%]; and Q4, 890 [1.2%], $P < 0.001$ by the Log-rank test). In multivariate models which were adjusted for age and sex in the model 1 and for clinical characteristics with borderline statistical significance along with age and sex in the model 2, the association between FLI quartile and HF incidence remained statistically significant in each model in the time-dependent Cox proportional hazard analysis (Table 3). When we used various cutoff-points were tried to categorize the study population, which were suggested by the previous studies ($0 \leq \text{FLI} < 30$, $30 \leq \text{FLI} < 60$, and $\text{FLI} \geq 60$, by Bedogni et al. [13]; $0 \leq \text{FLI} < 25$, $25 \leq \text{FLI} < 35$, and $\text{FLI} \geq 35$ for male, $0 \leq \text{FLI} < 10$, $10 \leq \text{FLI} < 20$, and $\text{FLI} \geq 20$ for female, by Yang et al. [15]). Regardless of the cutoff-points used, the highest FLI group had the highest risk for new onset HF (Supplementary Table 1).

Subgroup analysis

Adjusted HRs according to subgroups summarized in the figure 3. FLI was a significant determinant of new onset HF in all subgroups evaluated (**Figure 3**).

Discussion

In this study, we showed higher FLI, a well validated index of NAFLD, was associated with increased risk of new onset HF in healthy Korean adult population. In this study, we adopted multivariate models to control several confounding factors such as hypertension and diabetes, which are well-known risk factors for HF. We evaluated more direct associations

between NAFLD and HF after exclusion of hypertension and diabetes from the multivariate models. This association was found in most of the subgroups.

The association between fatty liver and HF has been observed in several studies [11, 12], and mildly elevated serum GGT levels in the absence of excessive alcohol consumption were long-term, independent predictors of incident HF in some large population-based studies [18-20]. Zhang et al. reported 37 had NAFLD defined by ultrasonography in 102 patients with HF with reduced ejection fraction (HFrEF) (36.3%) [12]. In the Framingham study, higher GGT level, even within the normal range, had a 1.71-fold risk of HF (95% CI=1.21-2.41) compared with participants with GGT concentrations less than the median [18]. Also, GGT improved the risk reclassification modestly (net reclassification index, 5.7%; P=0.01) in the HF prediction [18]. In a prospective cohort study performed in Finland including 18,353 men and 19,726 women who were 25-74 years of age, moderate to high concentrations of serum GGT (from the 50th to the 90th percentiles) were significantly associated with incident HF, and the predictive power was stronger in participants aged <60 years [20].

The presence of NAFLD was associated with higher BMI and left ventricular (LV) mass index, and had more severe LV fibrosis [12]. Other studies showed that patients with NAFLD had increased LV wall thickness and varying degrees of subclinical LV systolic or diastolic dysfunction [21, 22]. Increased LV wall thickness and fibrosis is a marker of LV diastolic dysfunction regardless of their symptoms. Jung et al. showed mild and moderate to severe NAFLD group had the higher risk of having abnormal LV relaxation compared with normal controls [21]. They showed increased odds ratios for abnormal LV relaxation [mild group: 1.29 (95% confidence interval: 1.15 - 1.46), moderate to severe group: 1.95 (95% confidence interval: 1.61 - 2.35)] and increased relative wall thickness (>0.42) [mild group: 1.26 (95% confidence interval: 1.05 - 1.52), moderate to severe group: 1.46 (95% confidence interval: 1.08 - 1.95)] in their cohort having 20,821 Korean adults received health check-ups. The proposed mechanism of increased LV wall thickness include insulin resistance [23], increased renin-angiotensin-aldosterone system (RAAS) [24], and endothelial dysfunction and inflammation [11]. Insulin resistance may contribute to the development of LV hypertrophy and HF through increased renal sodium retention and activation of the sympathetic nervous system [25, 26]. Increased sympathetic nervous system can also increase hepatic fibrosis [27]. Mediators of RAAS, especially angiotensin II and aldosterone, play important roles in the development of hypertension and HF. Also, angiotensin II can be expressed by activated human hepatic stellate cells,[24] and activated local RAAS increase hepatic injury and induce fibrosis through angiotensin II-mediated stimulation of fibroblast proliferation and increased release of inflammatory cytokines [28]. Endothelial dysfunction, as a component of inflammation, can increase arterial stiffness and LV afterload through increased vascular tone, sympathetic overactivity, and sodium retention [29]. Inflammation can promote coronary atherosclerosis and increase risk for cardiomyopathy and conduction abnormalities [11]. Inflammatory mediators also affect the progression of fatty liver disease via impaired fatty acid oxidation, increased oxidative stress, and local inflammation [30].

The presence of NAFLD was associated with poor prognosis of chronic HF [31] and acute HF [32]. Although mechanisms of the association between NAFLD and poor clinical outcomes of HF remains unclear, there are several proposed explanations including increased coronary atherosclerosis, enhancing LV hypertrophy and dysfunction, and increased aortic valve calcification [33-35]. Because liver plays an important role in the regulation of antioxidant and anti-inflammation systems [36], hepatic dysfunction can increase chronic inflammation and oxidative tissue injury in patient with HF [37] and the impaired antioxidant and antiinflammation roles of liver may further deteriorate the prognosis of HF patients [38].

Limitations

Our study has several limitations. First, we analyzed only claims data and National Health Screening data without echocardiographic or chemical data. Moreover, we estimated new onset HF by using the NHIS-NSC 2.0 database, which

is based on ICD-10 disease code, and the accuracy of HF diagnosis was not validated in this study. If we use echocardiographic data and serum biomarker including B-type natriuretic peptide or N terminal pro B-type natriuretic peptide, the diagnosis of HF would be accurate. Further studies should be needed to validate HF patients with health insurance data using either hospital-based medical records. Second, we demonstrated the simple relationship between increased FLI and increased new-onset HF and cannot show other contributable factors in the development of HF because this study is an observational study. Finally, this study population included only Koreans. Thus, caution should be needed in the generalization of this data to other ethnic populations.

Conclusions

Our findings demonstrated that higher FLI was independently associated with increased risk for HF in healthy Korean population.

Clinical Perspectives

Because control of metabolic syndrome and prevention of HF are important in the reduction of cardiovascular morbidity and mortality, the identification of increased HF risk may have important public health implications. Further studies are needed to document the effect of management of NAFLD not only on the risk of new onset HF, but also on the reduction of cardiovascular morbidity and mortality.

Declarations

Ethics approval and consent to participate

Institutional Review Board of Chungnam National University Hospital approved this study protocol (IRB No. 2019-10-053). Our IRB waived the requirement for informed consent.

Consent for publication

Not applicable

Availability of data and material

The datasets used and analyzed during the present study are available from the National Health Insurance Service. It can be used after acquisition of the right to use this data.

Competing interests

None. The authors have nothing to declare.

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AUTHOR CONTRIBUTIONS

RJH and PJH: study conception and design, acquisition of data, interpretation of data, drafting of manuscript, and critical revision; LHB: acquisition of data, analysis and interpretation of data; and YYH, KMS, KYG, PGM, LJH, and SIW: interpretation of data, and critical revision.

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Tables

Table 1. Baseline characteristics and laboratory findings

	FLI quartile				P-value	P for trend
	Q1	Q2	Q3	Q4		
Baseline characteristics						
Age, years	36.7±11.4	41.9±12.4	44.0±12.4	43.1±11.3	<0.001	<0.001
Male sex (%)	12,102(15.7)	30,737(39.8)	46,692(60.5)	62,507(81.0)	<0.001	<0.001
Height, cm	161.4±7.2	163.4±8.9	165.6±9.3	168.8±8.4	<0.001	<0.001
Weight, Kg	52.2±6.1	59.1±7.3	65.4±8.3	75.0±10.4	<0.001	<0.001
BMI, Kg/m ²	20.0±1.7	22.1±1.8	23.8±2.1	26.3±2.8	<0.001	<0.001
Waist circumference, cm	67.9±4.9	74.9±4.8	80.5±5.1	87.6±6.5	<0.001	<0.001
WHR, %	0.3±0.0	0.4±0.0	0.4±0.0	0.4±0.1	<0.001	<0.001
SBP, mmHg	111.0±11.1	115.4±11.1	118.6±10.6	121.8±10.0	<0.001	<0.001
DBP, mmHg	69.4±8.0	72.0±7.9	74.0±7.6	76.3±7.1	<0.001	<0.001
Smoking					<0.001	<0.001
Non-smoker	65,184(84.5)	53,779(69.7)	42,729(55.4)	28,355(36.8)		
Ex-smoker	3,609(4.7)	6,720(8.7)	10,711(13.9)	14,058(18.2)		
Current-smoker	8,350(10.8)	16,638(21.6)	23,713(30.7)	34,732(45.0)		
Alcohol consumption						
Amount, g/week	31.6±77.4	49.5±102.2	73.9±129.6	122.5 ±174.0	<0.001	<0.001
Activity, MET-min/week	346.7±350.8	379.7±382.7	388.8±388.1	374.6±373.4	<0.001	<0.001
Laboratory findings						
AST, IU/L	19.8±8.0	21.7±12.4	23.7±16.7	29.4±33.0	<0.001	<0.001
ALT, IU/L	14.5±8.9	17.9±12.2	22.9±22.2	36.3±50.5	<0.001	<0.001
GGT, IU/L	14.2±5.6	19.1±9.9	28.1±20.3	60.3±62.4	<0.001	<0.001
Hemoglobin, g/dL	13.0±1.4	13.6±1.6	14.2±1.6	14.9±1.4	<0.001	<0.001
Fasting glucose, mg/dL	87.9±9.5	90.3±10.2	92.2±10.7	94.8±11.4	<0.001	<0.001
Total cholesterol, mg/dL	176.9±33.6	187.1±35.9	196.2±39.3	207.0±40.7	<0.001	<0.001
Triglyceride, mg/dL	62.6±22.5	88.0±34.0	119.9±53.6	197.6±132.6	<0.001	<0.001
HDL cholesterol, mg/dL	64.1±24.8	59.3±19.9	55.5±25.8	51.7±32.0	<0.001	<0.001
LDL cholesterol, mg/dL	109.4±257.2	113.6±143.5	121.2±134.2	122.6±129.0	<0.001	<0.001
Creatinine, mg/dL	0.9±1.0	1.0±1.1	1.0±1.1	1.1±1.2	<0.001	<0.001
GFR, mL/min/1.73m ²	90.2±27.9	90.3±28.0	92.6±29.4	99.7±30.2	<0.001	<0.001

ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, DBP: diastolic blood pressure, GFR: glomerular filtration rate, GGT: gamma-glutamyl transferase, HDL: high-density lipoprotein, LDL: low-density lipoprotein, SBP: systolic blood pressure, WHR: waist-hip ratio

Table 2. Univariable analysis of new-onset heart failure

Characteristics	Value	N	HF (%)	HR	95% CI		P-value
					Lower	Upper	
Total	Total	308,578	2,532(0.8)				
Sex	Female	156,540	1,263(0.8)		Reference		
	Male	152,038	1,269(0.8)	1.113	1.030	1.204	0.007
Age, year	20-34	99,774	119(0.1)		Reference		
	35-49	130,099	637(0.5)	3.908	3.213	4.753	<0.001
	50-64	65,907	1,067(1.6)	12.536	10.371	15.153	<0.001
	65-74	10,374	497(4.8)	35.791	29.298	43.722	<0.001
	≥75	2,424	212(8.7)	75.652	60.429	94.711	<0.001
	Continuous			1.087	1.084	1.090	<0.001
BMI, Kg/m ²	<18.5	16,662	101(0.6)	1.075	0.870	1.328	0.505
	18.5-19.9	33,181	177(0.5)	0.929	0.786	1.098	0.390
	20-22.4	89,515	625(0.7)		Reference		
	22.5-24.9	90,961	814(0.9)	1.115	1.005	1.238	0.041
	≥25	78,259	815(1.0)	1.417	1.276	1.573	<0.001
	Continuous			1.058	1.045	1.072	<0.001
Smoking	Non-smoker	190,047	1,599(0.8)		Reference		
	Ex-smoker	35,098	320(0.9)	0.934	0.812	1.074	0.340
	Current-smoker	83,433	613(0.7)	1.120	0.997	1.259	0.057
Alcohol consumption, g/week	0	149,779	1,557(1.0)		Reference		
	≤140	110,537	626(0.6)	0.882	0.798	0.975	0.014
	>140	48,262	349(0.7)	0.991	0.871	1.126	0.890
	Continuous			1.000	1.000	1.000	0.960
SBP, mmHg	<120	165,193	1,019(0.6)		Reference		
	120-139	143,385	1,513(1.1)	1.295	1.195	1.404	<0.001
	Continuous			1.013	1.010	1.017	<0.001
DBP, mmHg	<80	210,638	1,513(0.7)		Reference		
	80-89	97,940	1,019(1.0)	1.220	1.126	1.322	<0.001
	Continuous			1.016	1.011	1.022	<0.001
FBS, mg/dL	< 100	246,415	1,876(0.8)		Reference		
	100 - 125	62,163	656(1.1)	1.042	0.953	1.140	0.370
	Continuous			1.003	1.000	1.007	0.058
Activity, MET-min/week	<500	221107	1871(0.8)				
	500-999	65361	453(0.7)	0.877	0.791	0.972	0.013
	≥1000	22110	208(0.9)	0.890	0.770	1.027	0.110
	Continuous			1.000	0.999	1.000	0.210
Waist circumference, cm	Continuous			1.027	1.022	1.032	<0.001
Total cholesterol, mg/dL	Continuous			1.001	1.000	1.002	<0.001
Triglyceride, mg/dL	Continuous			1.001	1.000	1.001	<0.001
HDL-cholesterol, mg/dL	Continuous			0.997	0.995	0.999	0.014
LDL-cholesterol, mg/dL	Continuous			1.000	1.000	1.000	0.290

BMI: body mass index, CI: confidential interval, DBP: diastolic blood pressure, FBS: fasting blood glucose, HDL: high-density lipoprotein, HF: heart failure, HR: hazard ration, LDL: low-density lipoprotein, MET: metabolic equivalent of task, SBP: systolic blood pressure

Table 3. Association between fatty liver index and new-onset heart failure

FLI	N.	New-onset HF	Univariate			Model 1*			Model 2 [†]		
			HR	95% CI	P- value	HR	95% CI	P- value	HR	95% CI	P- value
FLI quartile											
Q1 (0 - 4.9)	77,143	307(0.4)		Reference			Reference			Reference	
Q2 (5.0 - 12.5)	77,137	543(0.7)	1.691	1.470-1.945	<0.001	1.104	0.958-1.271	0.171	1.071	0.930-1.234	0.339
Q3 (12.6 - 31.0)	77,153	792(1.0)	2.409	2.112-2.748	<0.001	1.386	1.212-1.586	<0.001	1.314	1.147-1.504	<0.001
Q4 (> 31.0)	77,145	890(1.2)	2.709	2.380-3.085	<0.001	1.857	1.620-2.127	<0.001	1.710	1.489-1.964	<0.001

*Cox proportional hazard models including age, and sex as covariates

†Cox proportional hazard models including age, sex, and clinical characteristics, of which association with new-onset heart failure showed borderline statistical significance (P < 0.100)

CI: confidential interval, FLI: fatty liver index, HR: hazard ratio

Supplementary Table

Supplementary table 1. Association between fatty liver index and new-onset heart failure

FLI	N.	New-onset HF	Univariate			Model 1*			Model 2 [†]		
			HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
FLI criteria 1											
0 ≤ FLI < 30	228,136	1,608(0.7)	Reference			Reference			Reference		
30 ≤ FLI < 60	54,563	614(1.1)	1.538	1.402-1.688	<0.001	1.376	1.250-1.514	<0.001	1.320	1.198-1.453	<0.001
FLI ≥ 60	25,879	310(1.2)	1.669	1.478-1.885	<0.001	1.961	1.727-2.227	<0.001	1.849	1.622-2.106	<0.001
FLI criteria 2‡											
Low probability	178,464	10,20(0.6)	Reference			Reference			Reference		
Intermediate probability	46,892	480(1.0)	1.735	1.556-1.933	<0.001	1.233	1.105-1.376	<0.001	1.196	1.072-1.334	0.001
High probability	83,222	1,032(1.2)	2.104	1.930-2.294	<0.001	1.631	1.496-1.779	<0.001	1.557	1.423-1.704	<0.001

*Cox proportional hazard models including age, and sex as covariates

†Cox proportional hazard models including age, sex, and clinical characteristics, of which association with new onset heart failure showed borderline statistical significance (P < 0.100)

‡Low probability: $0 \leq \text{FLI} < 25$ for male, $0 \leq \text{FLI} < 10$ for female; intermediate probability: $25 \leq \text{FLI} < 35$ for male, $10 \leq \text{FLI} < 20$ for female; high probability: $\text{FLI} \geq 35$ for male, $\text{FLI} \geq 20$ for female
CI: confidential interval, FLI: fatty liver index, HR: hazard ratio

Figures

Figure 1

Overview of the study population

Figure 2

Cumulative incidence of new onset heart failure according to their quartiles. Statistical significance was determined using the log-rank test.

Figure 3

Forest plots of hazard ratios for new onset heart failure stratified by various clinical characteristics. CI = confidence interval; HR = hazard ratio.