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Original article

Association between nonalcoholic fatty liver disease and left ventricular diastolic dysfunction: A 7-year retrospective cohort study of 3,380 adults using serial echocardiography

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ABSTRACT

Aim: Left ventricular diastolic dysfunction (LVDD) has been observed in people with nonalcoholic fatty liver disease (NAFLD) in cross-sectional studies but the causal relationship is unclear. This study aimed to investigate the impact of NAFLD and the fibrotic progression of the disease on the development of LVDD, assessed by serial echocardiography, in a large population over a 7-year longitudinal setting.

Methods: This retrospective cohort study included the data of 3,380 subjects from a medical health check-up program. We defined subjects having NAFLD by abdominal ultrasonography and assessed significant liver fibrosis by the aspartate transaminase (AST) to platelet ratio index (APRI), the NAFLD fibrosis score (NFS), and the fibrosis-4 (FIB-4) index. LVDD was defined using serial echocardiography. A parametric Cox proportional hazards model was used.

Results: During 11,327 person-years of follow-up, there were 560 (16.0 %) incident cases of LVDD. After adjustment for multiple risk factors, subjects with NAFLD showed an increased adjusted hazard ratio (aHR) of 1.21 (95 % confidence interval [CI]=1.02–1.43) for incident LVDD compared to those without. The risk of LV diastolic dysfunction increased progressively with increasing degree of hepatic steatosis ($P < 0.001$). Compared to subjects without NAFLD, the multivariable-aHR (95 % CI) for LVDD in subjects with APRI < 0.5 and APRI ≥ 0.5 were 1.20 (1.01–1.42) and 1.36 (0.90–2.06), respectively ($P = 0.036$), while other fibrosis prediction models (NFS and FIB-4 index) showed insignificant results.

Conclusions: This study demonstrated that NAFLD was associated with an increased risk of LVDD in a large cohort. More severe forms of hepatic steatosis and/or significant liver fibrosis may increase the risk of developing LVDD.

Abbreviations: ALT, alanine aminotransferase; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; BMI, Body mass index; CI, Confidence interval; EF, ejection fraction; FIB-4, fibrosis-4; FLI, Fatty liver index; FPG, fasting plasma glucose; HF, Heart failure; HFpEF, HF with preserved EF; HFrEF, HF with reduced EF; HR, Hazard ratio; LV, left ventricular; LVDD, left ventricular diastolic dysfunction; NAFLD, Nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NFS, NAFLD fibrosis score; TTE, transthoracic echocardiography; US, ultrsasound.

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1. Introduction

Nonalcoholic fatty liver disease (NAFLD) has become the most common liver disease and its prevalence is increasing at an alarming rate, ranging from 15 % to 45 %, particularly high in the Americas and South-East Asia [1–3]. NAFLD has become the second most common reason for liver transplantation in Western countries [4]. It has emerged as one of the most challenging health issues and is associated with increased economic burdens [5].

NAFLD is defined by an excessive deposition of fat involving more than 5 % of hepatocytes without significant alcohol consumption and other secondary causes of liver steatosis [6]. It encompasses a broad spectrum of liver disease ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), a progressive form of hepatic damage, inflammation, and fibrosis [7]. NAFLD has been considered to be a multisystem disease [8]. For instance, cardiovascular disease is linked to a major cause of death in patients with NAFLD. Interestingly, most of the morbidity and mortality in patients with NAFLD do not result from progressive liver disease but are derived from the increased risk of cardiovascular disease [9–11].

In addition, growing evidence suggests a possible link between NAFLD and heart function [12,13]. Heart failure (HF) has become an important health issue in recent decades [14]. HF is a major cause for hospitalization [15] and markedly increases all-cause mortality. It is categorized according to left ventricular (LV) ejection fraction (EF) into either HF with reduced EF (HFrEF) or HF with preserved EF (HFpEF), also referred to as LV diastolic dysfunction. The diagnosis and management of HFrEF have been relatively well studied, whereas that of HFpEF has remained incompletely understood. LV diastolic dysfunction has important clinical implications since the prevalence is increasing and almost half of the patients with HF have HFpEF [16,17]. In addition, the prognosis and mortality rate of HFpEF have been similar to HFrEF [18,19]. Recent studies highlighted the potential benefits of dapagliflozin and empagliflozin in reducing the combined risk of worsening HF and cardiovascular death in patients with HFpEF [20,21]. As a result, these medications have been included as class I intervention in the new ESC 2023 guidelines for the treatment of HFpEF [22]. However, the identification of predisposing factors associated with HFpEF remains important for setting up effective prevention strategies.

Previous small cross-sectional studies demonstrated that people with NAFLD had altered LV structure and diastolic dysfunction [23–26]. Early features of LV diastolic dysfunction have been shown in patients with type 2 diabetes and NAFLD [27,28]. However, due to the predominantly cross-sectional design of most studies, the causal relationship between the two conditions has remained elusive. Recently, systematic review reported that NAFLD was associated with a 1.5-fold higher risk of heart failure with assessed mainly by International Classification of Diseases (ICD) codes [12]. Moreover, there has been limited study evaluating the casual association between hepatic fibrosis and subclinical myocardial dysfunction evaluated by echocardiography. Nevertheless, several underlying pathophysiological processes could potentially elevate the risk of HF in individuals with NAFLD [13]. Thus, this study aimed to investigate the longitudinal effects of hepatic steatosis and fibrosis by abdominal sonography and liver fibrosis prediction models on the development of LV diastolic dysfunction using serial echocardiography in a large population.

2. Materials and methods

2.1. Study population

In this longitudinal, retrospective cohort study, we included 6623 subjects aged ≥ 20 who underwent two or more serial screenings by echocardiography during annual or biennial medical health check-up programs from September 2006 through December 2013 at the Health Promotion Center of Samsung Medical Center, Seoul, Republic of Korea. Industrial Safety and Health Law in the Republic of Korea requires annual or biennial health screening examinations of all employees. The study population consisted of employees of various companies and organizations, and subjects who voluntarily took part in comprehensive health screening examinations at the center. We excluded 966 participants with missing data for echocardiographic parameters or laboratory results and those with diastolic dysfunction at baseline ($n = 548$). Participants with a LVEF of less than 50 % or moderate to severe valvular heart disease ($n = 48$) or an estimated glomerular filtration rate (eGFR) of less than 30 mL/min/1.73 m^2 ($n = 2$) or who have history of angina pectoris ($n = 130$) were also excluded. In addition, we excluded those with positive serologic markers of hepatitis B ($n = 237$) or hepatitis C ($n = 62$) viruses, those who have history of liver cancer ($n = 6$) or cirrhosis ($n = 115$), or daily alcohol consumption greater than 30 g for men and greater than 20 g for women ($n = 1129$) to define NAFLD. Finally, a total of 3380 participants were included in the analyses (Fig. 1). The study was approved by the Institutional Review Board (IRB) of Samsung Medical Center (IRB No. SMC 2020–04–122). Informed consent was waived by the IRB because the study information was de-identified.

2.2. Clinical and laboratory measurements

Medical history, smoking status, alcohol status, exercise status, medication, anthropometric data, and laboratory data were collected during routine health examinations. Smoking status was categorized as never, past, or current smoking. Exercise status was assessed as none or frequent exercise if any kind of physical exercise was performed (≥3 times per week). Blood pressure (BP) was measured using a mercury sphygmomanometer after at least five minutes of rest in a sitting position. Body mass index (BMI) was calculated as body weight divided by height squared (kg/m^2). Waist circumference was measured at the narrowest point between the upper iliac crest and the lowest rib after normal expiration [29].

Venous blood samples were obtained after a 12-hour overnight fast. Total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, aspartate aminotransferase (AST), and alanine aminotransferase (ALT), high-sensitivity C-reactive protein (hs-CRP), fasting plasma glucose, insulin, glycosylated hemoglobin (HbA1c) were measured. The estimated glomerular filtration rate (eGFR) and the homeostasis model assessment index for insulin resistance (HOMA-IR) were calculated. Detailed methods used in the measurement of blood laboratory profiles were as described in previous research [30].

Diabetes was defined as having a fasting plasma glucose (FPG) of 126 mg/dl or greater, HbA_{1c} of 6.5 % or greater, or current use of diabetes medication [31]. Hypertension was defined as having a blood pressure of 140/90 mmHg or more or taking antihypertensive medication [32]. Dyslipidemia was defined as LDL cholesterol level greater than 160 mg/dl or taking dyslipidemia medication.

2.3. Measurement of hepatic steatosis by abdominal ultrasound

Abdominal ultrasound (US) was performed using LogiQ E9 (GE Healthcare, Milwaukee, Wisconsin, USA), iU22 xMatrix (Philips Medical Systems, Cleveland, Ohio, USA), or ACUSON Sequoia 512 equipment (Siemens, Issaquah, Washington, USA) by experienced radiologists unaware of the study aims. A US diagnosis of fatty liver was established according to standard criteria, including parenchymal brightness, liver-to-kidney contrast, deep beam attenuation, and bright vessel walls [33,34]. To determine the degree of hepatic steatosis, we used the following quantitative grading system [35–38]: normal, hepatic parenchymal echogenicity is usually equal to that of the renal cortex; mild, diffuse slight increase in fine echoes in the hepatic parenchyma with normal visualization of the diaphragm and intrahepatic vessel borders; moderate, moderate diffuse increase in fine echoes with slightly impaired visualization of the intrahepatic vessels and diaphragm; severe, marked

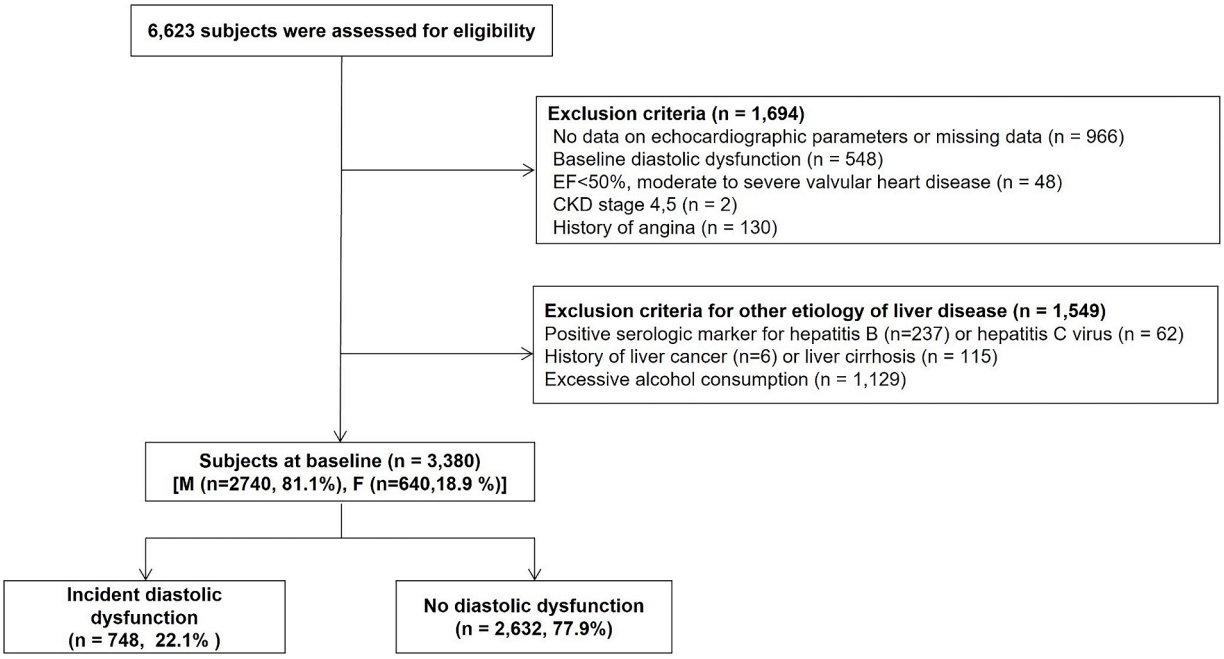

Fig. 1. Flowchart of the study population.
Abbreviations: CKD, chronic kidney disease; EF, ejection fraction; LV, left ventricular

increase in fine echoes with poor or no visualization of the intrahepatic vessel borders, diaphragm, and posterior portion of the right lobe of the liver.

2.4. Definition of nonalcoholic fatty liver disease

NAFLD was defined as the presence of hepatic steatosis in the absence of other identifiable liver disease including viral hepatitis B (n = 237) and C (n = 62), liver cirrhosis (n = 115), and liver cancer (n = 8) and excessive alcohol use ($\geq$ 30 g/day for men and $\geq$ 20 g/day for women; n = 1129; Fig. 1). We further used the ultrasound fatty liver index (US-FLI) which is a semiquantitative scoring system based on ultrasound findings [39]. According to this score, minimum US-FLI $\geq$2 diagnosed NAFLD, and severe NAFLD was defined by US-FLI $\geq$4 [40].

2.5. Definition of significant liver fibrosis

Among participants with NAFLD, the presence of advanced liver fibrosis was determined by previously validated liver fibrosis prediction models of AST to platelet ratio index (APRI), NAFLD fibrosis score (NFS), and the fibrosis-4 (FIB-4) index [41]. These were calculated with the following formula: APRI, [AST (U/L)/normal upper limit AST]/platelet count ($\times 10^9$/L) $\times$ 100 [42]; NFS, $-1.675+0.037 \times$ age (years)$+0.094 \times$ BMI (kg/m^2)$+1.13 \times$ [impaired fasting glucose or diabetes mellitus (yes=1, no=0)]$+0.99 \times$ AST/ALT$-0.013 \times$ platelet count ($\times 10^9$/L)$-0.66 \times$ albumin (g/dl) [43]; FIB-4, age (years) $\times$ AST (U/L)/[platelet count (10^9/L) $\times$ ALT (U/L)$^{1/2}$] [44]. A low APRI (< 0.5) is considered a strong predictor of the absence of liver fibrosis [45]. NFS was used to assess the severity of fibrosis [43] and to classify participants with NAFLD into two groups: high-intermediate (NFS ≥ -1.455) and low (NFS < -1.455) probability of advanced fibrosis. A low FIB-4 score ($<$ 1.3) is also a strong predictor of the absence of liver fibrosis [46].

2.6. Echocardiography and definition of LV diastolic dysfunction

The measurements of comprehensive echocardiography, including standard two-dimensional transthoracic echocardiography (TTE) and doppler echocardiography, were performed as part of a health promotion program by well-trained echocardiographers and clinicians as recommended by the 2003 American Society of Echocardiography (ASE) guideline and 2009 European Association of Echocardiography/ASE guidelines [47] with commercially available equipment (Vivid 7, GE Medical Systems, Milwaukee, WI, USA). Echogenic parameters including LVEF, left atrial (LA) volume index (LAVI) reflecting LA enlargement, transmitral early diastolic velocity (E), and mitral annulus early diastolic velocity (e′) were assessed. LVEF was assessed by biplane Simpson's rule via manual tracing of digital images [48]. LV diastolic dysfunction with normal EF was defined as preserved LVEF ($\geq$ 50 %) and one or more of the following findings on screening echocardiography; (1) E/e′ > 14, (2) $0.8 < E/A < 1.5$, $8 < E/e' \leq 14$, and e′ < 7, and (3) $8 < E/e' \leq 14$ and left atrial enlargement (LAVI > 34 ml/m^2) [49–53].

2.7. Statistical analysis

All continuous variables are presented as mean $\pm$ SD, and categorical variables are expressed as frequencies with percentages. Group differences were tested using the unpaired Student's t-test for continuous variables and the $\chi 2$ test for categorical variables. The endpoint of this study was the incident LV diastolic dysfunction. We have considered the presence of interval censoring because incident LV diastolic dysfunction develops at an unknown time point between the visit of diagnosis and the previous visit. Therefore, a flexible parametric Cox proportional hazards model was used to assess the relationship between NAFLD and incident LV diastolic dysfunction [54]. For multivariable-adjusted analyses, Model 1 was adjusted for age, sex, waist circumference, systolic BP, fasting plasma glucose, LDL cholesterol, and triglycerides. Model 2 was further adjusted for antidiabetic medications, use of antihypertensive medications, use of lipid lowering medications, exercise status, smoking status, and eGFR. Additionally, subgroup analyses were performed by age ($<$ 50, $\geq$ 50 years), sex, dyslipidemia, diabetes, hypertension, or BMI ($<$ 25, $\geq$ 25 kg/m^2). These models were fully adjusted for all confounders (Model 2). All the P values were two-tailed and those below 0.05 were considered statistically significant. Statistical analyses were performed using SPSS Version 26 (IBM Corp, Armonk, NY, USA) and STATA version 14 (StataCorp LP, College Station, TX, USA).

3. Results

3.1. Baseline characteristics

Table I shows clinical characteristics and laboratory variables of study participants according to the baseline status of NAFLD. The mean age was 53.1 ± 8.1 years, men comprised 82.1 %, and the prevalence of NAFLD at baseline was 36.7 % ($n = 1284$). Participants with NAFLD had higher baseline systolic BP, diastolic BP, waist circumference, BMI, total cholesterol, LDL cholesterol, triglycerides, AST, ALT, GGT, HbA_{1c}, FPG, fasting insulin, HOMA-IR, log CRP, and E/e′ ratio but lower HDL cholesterol, estimated GFR, septal e' velocity, and E/A ratio than those without NAFLD at baseline. There were no significant differences in age, or LVEF, between the two groups. The incidence of LV diastolic dysfunction was higher in participants with NAFLD than those without. In Table S1 (see supplementary materials associated with this article on line), individuals with incident LV diastolic dysfunction showed significantly higher baseline waist circumference, systolic BP, triglycerides, ALT, GGT, log CRP, and HOMA-IR values.

3.2. Association between NAFLD and development of LV diastolic dysfunction

There were 748 (22.1 %) incident cases of LV diastolic dysfunction during 10,916 person-years of follow-up. The cumulative incidence of LV diastolic dysfunction was significantly higher in subjects with NAFLD compared to those without (Fig. 2, $P < 0.0001$ by log-rank test). Table 2 shows the HRs and 95 % CIs for incident LV diastolic dysfunction according to the presence and degree of NAFLD. In Model 1, after adjustment for age, sex, waist circumference, systolic BP, fasting plasma glucose, LDL cholesterol, and triglycerides, the HRs (95 % CI) of incident LV diastolic dysfunction in participants with NAFLD compared to those without was 1.23 (1.04–1.46). In Model 2, after further adjustment for antidiabetic medications, use of antihypertensive medications, use of lipid lowering medications, exercise status, smoking status, and eGFR, HRs (95 % CI) of incident LV diastolic dysfunction in participants with NAFLD compared to those without was 1.21 (1.02–1.43) (Table II; Table S2: see supplementary materials associated with this article on line). In Model 2, the HRs (95 % CI) of incident LV diastolic dysfunction in participants with mild, moderate, and severe NAFLD compared to those without were 1.16 (0.96–1.42), 1.27 (1.01–1.59), and 1.80 (0.82–3.92), respectively. A tendency of increasing risk of incident LV diastolic dysfunction according to NAFLD degree was significant (P for trend < 0.001). In addition, when using the US-FLI score, a higher US-FLI score showed an increased aHR for LV diastolic dysfunction compared to a lower US-FLI score (P for trend $= 0.038$).

In stratified subgroup analyses, the positive association between NAFLD and incident LV diastolic dysfunction was consistent across all subgroups (Table S3: see supplementary materials associated with this article on line). NAFLD had no heterogeneous effect on diastolic dysfunction with age, sex, dyslipidemia, diabetes, hypertension, and BMI (P for interaction > 0.05).

3.3. Association between significant hepatic fibrosis in NAFLD and development of LV diastolic dysfunction

Compared to participants without NAFLD, the fully adjusted HRs (95 % CI) for incident LV diastolic dysfunction in participants with low APRI (< 0.5) and with high APRI (≥ 0.5) were 1.20 (1.01–1.42) and 1.36 (0.90–2.06), respectively (P for trend $= 0.036$) (Table III). However, when NAFLD participants were classified according to NFS or FIB-4, the association was not significant.

4. Discussion

In this study, we have demonstrated through data from a large 7-year

TABLE I
Baseline characteristics of study participants with and without nonalcoholic fatty liver disease (NAFLD).

NAFLD	No ($n = 2107$)	Yes ($n = 1273$)	Total ($n = 3380$)	*P*-value
Age (years)	54.5 ± 9.1	54.8 ± 9.1	54.6 ± 9.1	0.525
Men, *n* (%)	1633 (77.5)	1107 (87.0)	2740 (81.1)	< 0.001
Smoking status, *n* (%)				< 0.001
Non-smoker	755 (43.4)	351 (32.6)	1106 (39.3)	
Ex-smoker	584 (33.6)	371 (34.5)	955 (33.9)	
Current smoker	400 (23.0)	354 (32.9)	754 (26.8)	
Frequent exercise, *n* (%)	1000 (47.5)	514 (40.4)	1514 (44.8)	< 0.001
Systolic BP (mmHg)	118.1 ± 15.8	122.2 ± 15.9	119.6 ± 15.9	< 0.001
Diastolic BP (mmHg)	73.9 ± 10.9	77.2 ± 10.6	75.2 ± 10.9	< 0.001
Waist circumference (cm)	83.6 ± 7.4	90.1 ± 6.8	86.1 ± 7.9	< 0.001
Body mass index (kg/m^2)	23.5 ± 2.4	25.7 ± 2.5	24.3 ± 2.6	< 0.001
Total cholesterol (mg/dL)	193.4 ± 32.5	196.9 ± 33.1	194.7 ± 32.8	0.003
HDL cholesterol (mg/dL)	56.5 ± 13.9	49.0 ± 11.4	53.6 ± 13.5	< 0.001
LDL cholesterol (mg/dL)	120.6 ± 28.9	125.0 ± 29.3	122.3 ± 29.1	< 0.001
Triglycerides (mg/dL)	101.0 (76.0–138.0)	144.0 (106.0–203.0)	115.0 (84.0–162.0)	< 0.001
AST (U/L)	22.8 ± 8.4	26.4 ± 10.7	24.2 ± 9.5	< 0.001
ALT (U/L)	21.0 ± 10.2	31.6 ± 18.3	25.0 ± 14.7	< 0.001
GGT (U/L)	32.2 ± 29.4	49.6 ± 50.9	38.7 ± 39.8	< 0.001
Log CRP (mg/dL)	−1.2 ± 0.4	−1.1 ± 0.4	−1.1 ± 0.4	< 0.001
Glycemic status				
HbA_{1c} (%)	5.5 ± 0.6	5.8 ± 0.8	5.6 ± 0.7	< 0.001
Fasting plasma glucose (mg/dL)	94.5 ± 15.5	101.9 ± 20.0	97.3 ± 17.7	< 0.001
Fasting insulin (μIU/mL)	7.2 (5.4–9.5)	9.6 (7.3–12.9)	7.9 (6.0–10.8)	< 0.001
HOMA-IR	1.6 (1.2–2.2)	2.4 (1.7–3.2)	1.9 (1.4–2.6)	< 0.001
estimated GFR (mL/min/1.73 m^2)	81.2 ± 12.1	81.9 ± 12.9	81.5 ± 12.4	0.141
Medications				
Anti-hypertensive medication use, *n* (%)	433 (20.6)	410 (32.2)	843 (24.9)	< 0.001
Lipid-lowering drugs use, *n* (%)	338 (16.0)	338 (26.6)	676 (20.0)	0.004
Anti-diabetic medication use, n (%)	129 (6.1)	134 (10.5)	263 (7.8)	< 0.001
Echocardiography variables				
Septal e' (cm/s)	7.8 ± 2.2	7.5 ± 2.1	7.7 ± 2.1	< 0.001
LVEF (%)	66.1 ± 5.4	66.3 ± 5.2	66.1 ± 5.3	0.338
E/e′ ratio	7.2 ± 1.8	7.5 ± 1.8	7.3 ± 1.8	< 0.001
E/A ratio	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.3	< 0.001
LAVI (mL/m^2)	24.1 ± 7.3	24.2 ± 6.7	24.1 ± 7.1	0.667
LVMI (g/m^2)	85.2 ± 16.7	86.3 ± 16.6	85.6 ± 16.6	0.125
Incident diastolic dysfunction, *n* (%)	432 (20.5)	316 (24.8)	748 (22.1)	0.004

Continuous variables with normal distributions are expressed as mean ± standard deviation, whereas continuous variables with non-normal distributions are expressed as median (interquartile range). Categorical variables are expressed as percent (%).
Abbreviations: ALT, aspartate aminotransferase; AST, aspartate

aminotransferase; BP, blood pressure; CRP, C-reactive protein; GFR, glomerular filtration rate; GGT, gamma-glutamyltransferase; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; LAVI, left atrial volume index; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index.

longitudinal cohort that the risk of LV diastolic dysfunction evaluated by serial echocardiography increased in subjects with NAFLD compared to those without independently of other cardiovascular risk factors. Moreover, the risk was significantly increased in subjects with more severe forms of hepatic steatosis or significant liver fibrosis, as indicated by a higher APRI, but not by NFS or FIB-4 score.

Previous cross-sectional studies have reported a positive relationship between NAFLD and LV diastolic dysfunction [23,24]. A recent meta-analysis has also shown 2.02 fold increased odds of having LV diastolic dysfunction among individuals with NAFLD compared to those without, although there were different odds ratios (ORs) based on the country of origin in the subgroup analysis (western countries with ORs of 1.76 and eastern countries with ORs of 2.59) [55]. In addition, one longitudinal study reported that NAFLD is associated with subclinical changes in myocardial structure and function after a 5-year follow-up independent of the traditional risk factors [56]. This study presented ORs and linear regression analyses of a 1827 study population for the association of baseline NAFLD and the cardiac changes at a 5-year follow-up. Since NAFLD has a vast spectrum including simple hepatic steatosis, steatohepatitis, and fibrosis [57–59], we hypothesized that the effects of NAFLD on incident LV diastolic dysfunction might vary according to its severity. Previous cross-sectional studies showed an increased risk of LV diastolic dysfunction according to the degree of NAFLD on US [25] and a similar risk increased according to the grade of fibrosis using NFS [26]. Our study found causal relationships of NAFLD with subclinical myocardial dysfunction, indicated by HR during a long 7.5-year follow-up period in a large 3496 study population. In addition, we demonstrated that moderate and severe forms of hepatic steatosis by US or higher values of APRI were associated with a greater risk of developing LV diastolic dysfunction in a longitudinal cohort. However, compared with significant associations with high APRI and LV diastolic dysfunction, the NFS and FIB-4 index models did not show significant results, and future studies with larger numbers and longer follow-up periods are needed.

Certain underlying mechanisms have been suggested, although the exact pathophysiologic mechanisms linking NAFLD to incident LV diastolic dysfunction remain unclear. One plausible mechanism might be a systemic inflammatory condition. Indeed, NAFLD has been characterized by increased markers of chronic inflammation such as hs-CRP [60,61], which is related to coronary microvascular endothelial inflammation and oxidative stress [62]. Our results also showed that participants with NAFLD had higher baseline log hs-CRP than those without. In addition, advanced hepatic fibrosis is also related to inflammatory releasing proinflammatory cytokines (e.g., interleukin-6, tumor necrosis

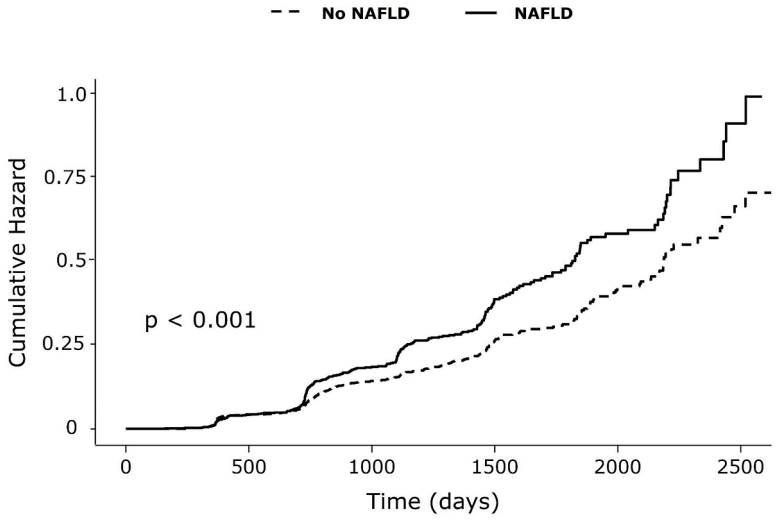

Fig. 2. Cumulative hazard of left ventricular diastolic dysfunction by nonalcoholic fatty liver disease (NAFLD) status at baseline.

TABLE II
Hazard ratios for incident left ventricular diastolic dysfunction according to presence and degree of nonalcoholic fatty liver disease (NAFLD).

	Subject, *n*	Case, *n* (%)	Crude	Model 1 HR (95 % CI)	Model 2 HR (95 % CI)
No NAFLD	2107	432 (20.5)	1 (reference)	1 (reference)	1 (reference)
NAFLD	1273	316 (24.8)	1.34(1.16–1.55)	1.23(1.04–1.46)	1.21 (1.02–1.43)
Mild	720	166 (23.1)	1.24 (1.03–1.48)	1.19 (0.97–1.44)	1.16 (0.96–1.42)
Moderate	531	143 (26.9)	1.46 (1.21–1.76)	1.31 (1.05–1.64)	1.27 (1.01–1.59)
Severe	22	7 (31.8)	2.34 (1.11–4.93)	1.71 (0.78–3.73)	1.80 (0.82–3.92)
p for trend			< 0.001	< 0.001	< 0.001
NAFLD	1273	316 (24.8)	1.34 (1.16–1.55)	1.23 (1.040–1.46)	1.21 (1.02–1.43)
US-FLI (2–3)	1251	309 (24.7)	1.33 (1.15–1.54)	1.22 (1.03–1.45)	1.20 (1.01–1.43)
US-FLI (≥4)	22	7 (31.8)	2.34 (1.11–4.93)	1.71 (0.78–3.73)	1.80 (0.82–3.92)
p for trend			< 0.001	0.012	0.038

Model 1: adjusted for age, sex, waist circumference, systolic BP, fasting plasma glucose, LDL cholesterol, and triglycerides.
Model 2: adjusted for Model 1 plus use of antidiabetic medications, use of antihypertensive medications, use of lipid lowering medications, exercise status, smoking status, and eGFR.
Abbreviations: BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratios; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; US-FLI, ultrasound fatty liver index.

Table III
Hazard ratios for incident left ventricular diastolic dysfunction according to the presence of significant hepatic fibrosis based on a liver fibrosis prediction model.

	Subject, n	Case, n (%)	Crude	Model 1 HR (95 % CI)	Model 2 HR (95 % CI)
No NAFLD	2107	432 (20.5)	1 (reference)	1 (reference)	1 (reference)
NAFLD with APRI < 0.5	1176	288 (24.5)	1.32 (1.14–1.53)	1.22 (1.03–1.46)	1.20 (1.01–1.42)
NAFLD with APRI ≥ 0.5	97	28 (28.9)	1.64 (1.12–2.40)	1.40 (0.93–2.10)	1.36 (0.90–2.06)
p for trend			<0.001	0.013	0.036
No NAFLD	2107	432 (20.5)	1 (reference)	1 (reference)	1 (reference)
NAFLD with NFS < −1.455	782	189 (24.2)	1.25 (1.05–1.48)	1.25 (1.04–1.50)	1.23 (1.02–1.48)
NAFLD with NFS ≥ −1.455	491	127 (25.9)	1.51 (1.24–1.85)	1.24 (0.99–1.56)	1.21 (0.96–1.52)
p for trend			<0.001	0.057	0.520
No NAFLD	2107	432 (20.5)	1 (reference)	1 (reference)	1 (reference)
NAFLD with FIB-4 < 1.3	860	222 (25.8)	1.36 (1.15–1.60)	1.27 (1.05–1.53)	1.26 (1.05–1.52)
NAFLD with FIB-4 ≥ 1.3	413	94 (22.8)	1.31 (1.04–1.63)	1.12 (0.88–1.44)	1.08 (0.84–1.39)
p for trend			<0.001	0.101	0.793

Model 1: adjusted for age, sex, waist circumference, systolic BP, fasting plasma glucose, LDL cholesterol, and triglycerides.
Model 2: adjusted for Model 1 plus use of antidiabetic medications, use of antihypertensive medications, use of lipid lowering medications, exercise status, smoking status, and eGFR.
For the NFS analyses, the models were not adjusted for age, fasting plasma glucose, and use of antidiabetic medications as these factors are included in the calculation of the NFS. In FIB-4 analyses, the models were not adjusted for age as this factor is included in the calculation of FIB-4.
Abbreviations: APRI, aspartate aminotransferase (AST) to platelet ratio index; BP, blood pressure; CI, confidence interval; FIB-4, fibrosis-4 score; eGFR, estimated glomerular filtration rate; HR, hazard ratios; LDL, low-density lipoprotein; NAFLD, non-alcoholic fatty liver disease.

factor-α, etc.) and dysregulated hepatokines (e.g., fetuin-A, RBP4, etc.) that can trigger myocardial oxidative stress, myocardial tissue alterations, fibrosis, and eventually LV diastolic stiffness [13,63,64]. The other possible mechanism linking NAFLD and incident LV diastolic dysfunction is insulin resistance [65]. A previous study found that hepatic steatosis and fibrosis were associated with LV diastolic dysfunction and that hepatic fibrosis was correlated with impaired myocardial glucose uptake when evaluated by [^{18}F]-fluorodeoxyglucose-positron emission tomography [66]. As insulin regulates myocardial glucose uptake, insulin resistance could hamper glucose utilization in myocytes and impair mitochondrial function and eventually contribute to LV diastolic dysfunction [67]. Moreover, since insulin is involved in protein synthesis, long-chain fatty acid metabolism, and vascular tone, hyperinsulinemia and insulin resistance can cause alterations in vascular homeostasis and inflammation that might be related to myocardial dysfunction [68–71].

There are several limitations to this study that need to be considered when interpreting these results. First, participants were selected from a single center; thus, they might not be representative of the general population. Hence, the possibility of selection bias and limitations through the generalization of the results should be considered. Second, since this study had a long duration and many participants, different radiologists and echocardiographers were involved in performing the abdominal US and echocardiography; this could lead to variability in measurement. Therefore, we additionally used the US-FLI, which is a semiquantitative scoring system based on ultrasound findings [39]. Third, the assessment of the presence and degree of NAFLD and significant hepatic fibrosis was not confirmed by liver biopsy, which is considered the gold standard, but liver biopsy is difficult to perform in large populations. Instead, we used APRI, NFS, and FIB-4 score as a liver fibrosis prediction model, which have been well validated in previous studies as well as in US findings [72,73]. However, the fibrosis prediction models showed the inherent in those with diabetes and in the elderly individuals [74,75]. In addition, regarding the definition of LV diastolic dysfunction by echocardiography, we could not adopt the criteria from the 2016 guideline [76] due to the lack of tricuspid values for all study participants. Although previous studies reported that there are sex differences in the prevalence, risk factors, and clinical outcomes of NAFLD [77], because of the relatively small proportion of women in this study, sex-based analysis of data was not shown. Therefore, we performed subgroup analysis and there was no interaction in sex subgroup, but the further study with the sufficient number of women is needed in the future. Lastly, we did not include information about dietary habits or intakes of nutritional supplements, although we adjusted for various potential confounders.

Nonetheless, the strengths of this study lie in its comprehensive design with a large longitudinal sample size with abdominal ultrasonographic data, serial echocardiographic data, and broad biochemical laboratory results of 3380 subjects which enable the investigation of the association between NAFLD and the development of LV diastolic dysfunction after adjusting for multiple metabolic risk factors. Although most previous large studies defined HF as a diagnostic code, we defined it using serial echocardiographic index, which could be more accurate. Furthermore, we used a quantitative grading system with abdominal US to assess the degree of fatty infiltration.

In summary, NAFLD was associated with an increased risk of developing LV diastolic dysfunction independently of the established risk factors, and this relationship was progressive with the increased severity of hepatic steatosis. These findings suggest that careful monitoring of patients with NAFLD and/or significant hepatic fibrosis for incident LV diastolic dysfunction may be useful in clinical practice.

CRediT authorship contribution statement

Gyuri Kim: Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Tae Yang Yu:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jae Hwan Jee:** Writing – review & editing, Data curation. **Ji Cheol Bae:** Writing – review & editing, Investigation, Data curation. **Mira Kang:** Writing – review & editing, Supervision, Investigation, Data curation, Conceptualization. **Jae Hyeon Kim:** Writing – review & editing, Supervision, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.diabet.2024.101534.

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