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ORIGINAL ARTICLE
Vascular and cardiac imaging

Association between non-alcoholic fatty liver disease and subclinical left ventricular dysfunction in the general population

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Aims Emerging evidence suggests an association between non-alcoholic fatty liver disease (NAFLD) and heart failure (HF). We investigated the relationship between NAFLD and left ventricular (LV) functional remodelling in a general population sample without overt cardiac and liver disease.

Methods and results We included 481 individuals without significant alcohol consumption who voluntarily underwent an extensive cardiovascular health check. The fatty liver index (FLI) was calculated for each participant, and NAFLD was defined as FLI $\geq$ 60. All participants underwent 2D transthoracic echocardiography; LV global longitudinal strain (LVGLS) was assessed with speckle-tracking analysis. Univariable and multivariable linear regression models were constructed to investigate the possible association between NAFLD and LVGLS. Seventy-one (14.8%) participants were diagnosed with NAFLD. Individuals with NAFLD exhibited larger LV size and LV mass index than those without NAFLD, although left atrial size and *E*/*e*′ ratio did not differ between groups. Left ventricular global longitudinal strain was significantly reduced in participants with vs. without NAFLD (17.1% ± 2.4% vs. 19.5% ± 3.1%, respectively; $P < 0.001$). The NAFLD group had a significantly higher frequency of abnormal LVGLS (<16%) than the non-NAFLD group (31.0% vs. 10.7%, respectively; $P < 0.001$). Multivariable linear regression analysis demonstrated that higher FLI score was significantly associated with impaired LVGLS independent of age, sex, conventional cardiovascular risk factors, and echocardiographic parameters (standardized β −0.11, $P = 0.031$).

Conclusion In the general population without overt cardiac and liver disease, the presence of NAFLD was significantly associated with subclinical LV dysfunction, which may partly explain the elevated risk of HF in individuals with NAFLD.

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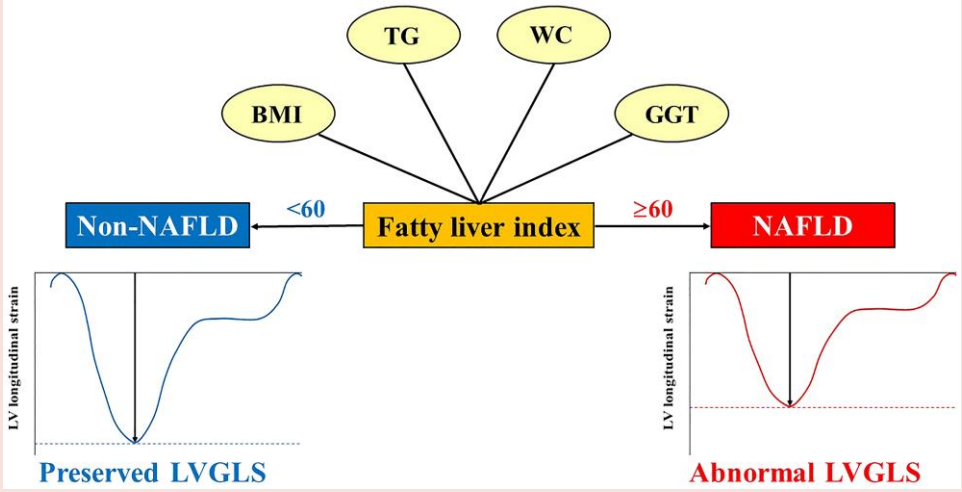
Graphical Abstract



Keywords Fatty liver index • Non-alcoholic fatty liver disease • Left ventricular global longitudinal strain • Speckle-tracking echocardiography

Introduction

Heart failure (HF) is a major public and economic health concern, and its incidence is increasing worldwide with the aging of societies.[1] Although various clinical risk factors and comorbidities, such as metabolic disorders and structural heart diseases, have been identified and treated,[1,2] patients with HF still exhibit a poor prognosis, with the 5-year mortality rate ranging from 60 to 75%.[3,4] These observations highlight the need for the identification of other modifiable risk factors that may allow preventive therapeutic interventions. Results of recent epidemiological studies have demonstrated a close relationship between non-alcoholic fatty liver disease (NAFLD) and HF, which is independent of traditional cardiovascular risk factors.[5–8] Non-alcoholic fatty liver disease is the most common liver disease involved in metabolic disorders, and it is characterized by hepatic steatosis without a secondary cause of hepatic fat accumulation.[9] Global NAFLD prevalence is as high as 25%.[10] The detection of NAFLD by an invasive method (i.e. liver biopsy) or by non-invasive imaging modalities [i.e. computed tomography (CT) and magnetic resonance imaging (MRI)] is somewhat difficult in routine clinical practice because of the enormous medical costs and technical issues.[9] The recently developed fatty liver index (FLI) is a simple and well-validated NAFLD risk score that includes body metrics and laboratory parameters and allows for a more feasible and cost-effective assessment of hepatic steatosis than conventional diagnostic approaches, especially in subclinical settings.[11–13]

Adverse myocardial structural and functional remodelling is a pivotal process in the development of HF. 2D speckle-tracking echocardiography has emerged as a sensitive tool for detecting early myocardial dysfunction.[14–16] Deterioration of left ventricular global longitudinal strain (LVGLS) precedes the reduction of LV ejection fraction, serving as a promising prognostic marker for HF in various clinical settings.[14,15,17] Exploring the possible association between NAFLD and subclinical LV systolic abnormalities assessed by LVGLS may enhance our understanding of the mechanisms linking NAFLD and HF and provide valuable information for preventive strategies for HF occurrence. The aim of the present study was to investigate the relationship between the NAFLD risk score and subclinical LV systolic dysfunction in a sample of the general population without overt cardiac and liver disease.

Methods

Study population

We initially enrolled 572 consecutive asymptomatic individuals who underwent an extensive cardiovascular health examination, including blood tests and transthoracic echocardiography, between June 2018 and May 2019. All participants gave informed consent that allowed all de-identified data, including laboratory tests and echocardiographic examinations, to be used for research purposes at the time of the health check-up. Exclusion criteria were as follows: (i) history of atrial fibrillation or flutter ($n = 7$), (ii) history of coronary artery disease ($n = 17$), (iii) reduced LV systolic function (LV ejection fraction < 50%) or moderate or severe mitral/aortic valvular disease ($n = 6$), (iv) prevalent liver disease ($n = 10$), (v) significant alcohol consumption according to the guideline of NAFLD[9] (>21 standard drinks per week in men and >14 standard drinks per week in women over the 2-year period preceding enrolment; $n = 48$), and (vi) suboptimal echocardiographic image quality ($n = 3$). Thus, 481 study participants free of cardiac and liver disease were included for analysis. This study was approved by the Institutional Review Board of the University of Tokyo (2019279NI), and the investigation conformed to the principles outlined in the Declaration of Helsinki.

Risk factor assessment and laboratory examination

Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or the use of antihypertensive agents. Diabetes mellitus was determined by a fasting glucose ≥126 mg/dL or the current use of insulin or hypoglycaemic drugs. Dyslipidaemia was defined as total serum cholesterol >240 mg/dL or receiving lipid-lowering

medications. Body mass index (BMI) was calculated based on height and weight (kg/m^2), and obesity was defined as BMI ≥ 25 kg/m^2 according to the WHO criteria for Asians.[18] Waist circumference was measured at the level of the umbilicus. Habitual alcohol consumption was defined alcoholic intake ≤21 units for men or 14 units for women per week.[9] Venous blood samples were obtained in the fasting condition. Serum aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), glucose, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, creatinine, and C-reactive protein were evaluated in all participants. The estimated glomerular filtration rate (eGFR) was computed with the abbreviated Modification of Diet in Renal Disease (MDRD) equation: eGFR (mL/min/1.73 m^2) = 194 × (serum creatinine)$^{-1.094}$ × (age)$^{-0.287}$ × (0.739 if woman).

Assessment of non-alcoholic fatty liver disease

The diagnosis of NAFLD was based on the FLI, which was calculated as follows[11]:

$$FLI = (e^{0.953\times\log_e(\text{triglycerides})+0.139\times BMI+0.718\times\log_e(GGT)+0.053\times\text{waist circumference}-15.745})/(1+e^{0.953\times\log_e(\text{triglycerides})+0.139\times BMI+0.718\times\log_e(GGT)+0.053\times\text{waist circumference}-15.745})\times 100.$$

Non-alcoholic fatty liver disease was defined as FLI ≥ 60 according to previous studies.[11–13]

Echocardiography

Standard echocardiography

All participants underwent standard 2D transthoracic echocardiography with a commercially available ultrasound system (Aplio, Canon Medical System Corp, Japan). All images were obtained by trained and registered cardiac sonographers who were blinded to other clinical information. Linear dimensions were measured in accordance with the guideline.[19] Left ventricular mass was calculated by a validated formula: LV mass = 0.8 × 1.04 × ([LV end-diastolic dimension + posterior wall thickness + interventricular septum thickness]^3 – [LV end-diastolic dimension]^3) + 0.6.[19] Left ventricular ejection fraction and left atrium (LA) volume were measured with the biplane Simpson's method.[19] Left ventricular mass and LA volume were indexed for body surface area. Peak early (*E*) diastolic velocity was assessed by transmitral spectral Doppler analysis. Peak early diastolic velocity (*e*′) of the septal and lateral mitral annulus was acquired from tissue Doppler imaging and averaged. The *E*/*e*′ ratio was then calculated.[20]

Speckle-tracking echocardiography

Speckle-tracking analysis was performed offline with vendor-independent and commercially available software (2D Cardiac Performance Analysis; Tomtec Imaging System, Germany). Left ventricular borders were detected semi-automatically and tracked throughout the entire cardiac cycle. Manual correction was performed in case of inaccurate endocardial detection. Left ventricular global longitudinal strain was calculated by averaging the negative peak value of longitudinal strain from all three apical views, including the four-chamber, two-chamber, and long-axis views.[15,16] Abnormal LVGLS was defined as LVGLS < 16.0%, based on previous studies in which impaired LVGLS carried significant and independent risk for incident HF.[14,15]

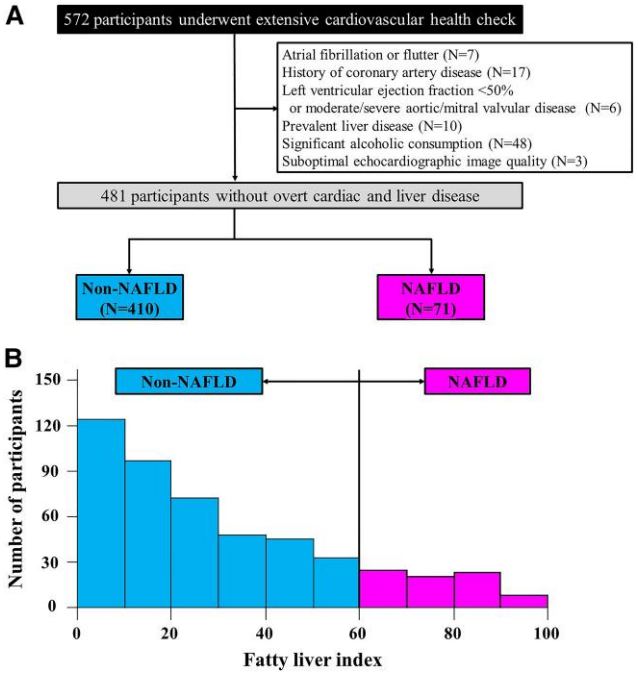


Figure 1 Flow chart of the study population (*A*). Distribution of study participants according to the fatty liver index (*B*). NAFLD, non-alcoholic fatty liver disease.

Table 1 Baseline clinical characteristics and laboratory parameters

	NAFLD ($n = 71$)	No NAFLD ($n = 410$)	*P* value
Age, years	56 ± 10	57 ± 10	0.078
Men, *n* (%)	67 (94.4)	259 (63.2)	<0.001
Body mass index, kg/m^2	27.4 ± 2.9	22.9 ± 2.6	<0.001
Waist circumference, cm	96.6 ± 6.3	83.7 ± 7.7	<0.001
Systolic blood pressure, mmHg	126 ± 12	118 ± 15	<0.001
Diastolic blood pressure, mmHg	82 ± 8	75 ± 9	<0.001
Hypertension, *n* (%)	32 (45.1)	102 (24.9)	<0.001
Diabetes mellitus, *n* (%)	14 (19.7)	25 (6.1)	<0.001
Dyslipidaemia, *n* (%)	35 (49.3)	136 (33.2)	0.009
Current smoking, *n* (%)	33 (46.5)	77 (18.8)	<0.001
Habitual alcohol consumption, *n* (%)	58 (81.7)	229 (55.9)	<0.001
Medications			
RAAS blockers, *n* (%)	15 (21.1)	59 (14.4)	0.146
Calcium channel blockers, *n* (%)	17 (23.9)	42 (10.2)	0.001
Statins, *n* (%)	19 (26.8)	71 (17.3)	0.060
Other lipid-lowering drugs, *n* (%)	11 (15.5)	18 (4.4)	<0.001
Oral anti-diabetic agents, *n* (%)	11 (15.5)	21 (5.1)	0.001
Laboratory data			
AST, U/L	27 (20–34)	21 (17–25)	<0.001
ALT, U/L	33 (23–51)	18 (14–23)	<0.001
GGT, U/L	71 (43–138)	24 (17–35)	<0.001
eGFR, mL/min/1.73 m^2	74 (68–83)	75 (67–84)	0.650
Total cholesterol, mg/dL	202 (177–226)	201 (180–226)	0.745
HDL cholesterol, mg/dL	50 (43–60)	66 (55–77)	<0.001
LDL cholesterol, mg/dL	121 (95–136)	119 (100–141)	0.458
Triglyceride, mg/dL	169 (134–281)	81 (60–117)	<0.001
Fasting blood glucose, mg/dL	105 ± 17	94 ± 10	<0.001
HbA1c, %	6.1 ± 0.7	5.7 ± 0.5	<0.001
C-reactive protein, mg/dL	0.08 (0.05–0.11)	0.04 (0.02–0.07)	<0.001
Fatty liver index	77.3 (67.1–85.5)	18.6 (8.5–33.0)	N/A

ALT, alanine transaminase; AST, aspartate transaminase; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; N/A, not applicable; NAFLD, non-alcoholic fatty liver disease; RAAS, renin–angiotensin–aldosterone system.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median (interquartile range) and compared with an unpaired *t*-test or Mann–Whitney *U* test as appropriate. Categorical variables were displayed as numbers and proportions and analysed with the χ^2 test or Fisher's exact test. Baseline characteristics and echocardiographic parameters were compared according to the presence or absence of NAFLD. The association between NAFLD risk score and LVGLS was examined in univariable and multivariable linear regression analyses. The factors related at the $P < 0.05$ level were selected as independent variables for multivariable analysis. A value of $P < 0.05$ was considered significant. All statistical analyses were performed with JMP 16 software (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics

Among the 481 study participants, the mean age was 57 ± 10 years and 326 (67.8%) were men. The median FLI (25th–75th percentile) was 22.7 (9.9–45.7), and 71 (14.8%) participants were categorized as having NAFLD (*Figure 1*). Baseline characteristics and laboratory parameters according to the presence or absence of NAFLD are displayed in *Table 1*. Participants with NAFLD were more likely to be men and had a larger BMI and waist circumference compared with the non-NAFLD group (all $P < 0.05$). They also exhibited a greater frequency of metabolic disorders (i.e. hypertension, diabetes mellitus, and dyslipidaemia), current smoking, and habitual alcohol consumption. As for laboratory parameters, individuals with NAFLD had higher levels of AST, ALT, and GGT, worse glycaemic profiles, and elevated C-reactive protein levels compared with individuals without NAFLD.

Echocardiographic measurements

Table 2 shows the echocardiographic measurements. Participants with NAFLD had larger LV diameters and LV mass index. The LV ejection fraction tended to be lower in individuals with NAFLD, although all study participants had a normal LV ejection

fraction (≥50%). Left atrium volume and *E*/e′ ratio did not differ between groups. In speckle-tracking analysis, individuals with NAFLD had significantly reduced LVGLS compared with the non-NAFLD group (17.1% ± 2.4% vs. 19.5% ± 3.1%; $P < 0.001$). Consistent with that observation, the FLI was negatively correlated with LVGLS ($r = -0.48$, $P < 0.001$; *Figure 2A*), and the NAFLD group exhibited a significantly higher prevalence of abnormal LVGLS (<16.0%) than the non-NAFLD group (31.0% vs. 10.7%; $P < 0.001$; *Figure 2B*).

Association between non-alcoholic fatty liver disease risk score and left ventricular global longitudinal strain

Results of univariable and multivariable linear regression analyses to investigate the association between NAFLD risk score and subclinical LV dysfunction are shown in *Table 3*. Univariable analysis demonstrated FLI to be associated with LVGLS (standardized β; −0.48, 95% confidence interval; −3.85 to −2.77, $P < 0.001$). In multivariable analysis adjusted for variables associated with LVGLS in univariable analyses, FLI was independently associated with LVGLS (standardized β; −0.11, 95% confidence interval; −1.44 to −0.07, $P = 0.031$). Representative cases are presented in *Figure 3*. The right case with NAFLD (FLI 81.6) had reduced LVGLS compared with the left case without NAFLD (FLI 23.6).

Table 2 Echocardiographic parameters stratified by the presence or absence of non-alcoholic fatty liver disease

	NAFLD ($n = 71$)	No NAFLD ($n = 410$)	*P* value
LV end-diastolic diameter, mm	45.9 ± 4.4	44.0 ± 4.1	0.001
LV end-systolic diameter, mm	29.7 ± 3.7	28.1 ± 3.2	0.002
LV ejection fraction, %	59.7 ± 5.1	63.1 ± 5.5	<0.001
LV mass index, g/m^2	69.2 ± 14.0	64.5 ± 15.7	0.005
Relative wall thickness	0.37 ± 0.07	0.34 ± 0.05	0.001
E-wave, cm/s	60.7 ± 10.6	65.6 ± 12.9	0.007
A-wave, cm/s	60.8 ± 13.7	58.1 ± 14.7	0.085
E/*A* ratio	1.0 ± 0.3	1.2 ± 0.4	0.002
e′ velocity, cm/s	7.2 ± 1.6	8.1 ± 2.0	<0.001
E/e′ ratio	8.8 ± 2.1	8.4 ± 2.1	0.071
LA volume index, mL/m^2	21.9 ± 5.3	21.9 ± 5.5	0.804
LVGLS, %	17.1 ± 2.4	19.5 ± 3.1	<0.001

A, late diastolic transmitral flow velocity; *E*, early diastolic transmitral flow velocity; e′, early diastolic mitral annular velocity; LA, left atrium; LV, left ventricle; LVGLS, left ventricular global longitudinal strain; NAFLD, non-alcoholic fatty liver disease.

Reproducibility analysis

Excellent correlations were observed in the inter- and intra-observer variability analysis of LVGLS ($r = 0.93$ and $r = 0.94$, respectively) in 15 randomly selected participants. Bland–Altman analysis showed that the inter- and intra-observer variabilities were −0.6 ± 1.3 and 0.2 ± 1.4%, respectively (mean ± 1.96 SD).

Discussion

The present study found that individuals with NAFLD assessed with the FLI had significantly impaired LVGLS compared with individuals without NAFLD in a general population sample free of overt cardiac and liver disease. Higher NAFLD risk score was associated with impaired LVGLS independent of conventional cardiovascular risk factors, pertinent biomarkers, and other echocardiographic measures.

Non-alcoholic fatty liver disease, left ventricular remodelling, and incident heart failure

Non-alcoholic fatty liver disease is the most common liver disease worldwide, affecting 1.7 billion individuals.[9,10] Recent epidemiological studies have reported that NAFLD is an independent risk factor for HF.[5–8,21] Fudim *et al.*[7] showed that among Medicare beneficiaries in the USA, patients with NAFLD had a 25% higher risk of developing HF. Roh *et al.*[6] and Park *et al.*[21] also demonstrated a positive correlation between the FLI and HF incidence in a Korean nationwide community-based study. Left ventricular global longitudinal strain assessed by speckle-tracking echocardiography is a reliable tool for the early detection of subclinical LV abnormalities[15,16] and has been confirmed as an excellent precursor to HF in various clinical settings.[14,15,17] The present study found that the prevalence of abnormal LVGLS was three-fold greater in individuals with NAFLD compared with those without it, even in individuals free of cardiac disease. Furthermore, the relationship between NAFLD risk score and reduced LVGLS was independent of traditional cardiovascular risk factors, biomarkers, and other echocardiographic parameters. Our findings are in line with previous investigations showing that patients with CT-assessed or biopsy-proven NAFLD had reduced LVGLS.[22,23] The present study evaluated the presence of NAFLD using a simple, cost-effective, and non-invasively derived score, allowing for widespread use of our observations.

Mechanisms linking non-alcoholic fatty liver disease and impaired left ventricular global longitudinal strain

Several possible mechanisms may account for the pathophysiological link between NAFLD and subclinical LV systolic dysfunction. First, enhanced systemic inflammation in individuals with NAFLD[24,25] may contribute to impaired coronary microcirculation leading to LV longitudinal systolic abnormalities.[26,27] Second, impaired myocardial glucose uptake accompanied by insulin resistance could shift toward fatty acid metabolism, which may result in deterioration of myocardial contractility through lipotoxicity and oxidative stress.[28,29] Finally, neurohormonal dysregulation, including the activation of the renin–angiotensin–aldosterone system and cardiac autonomic dysfunction, may also adversely affect LV systolic function in patients with NAFLD.[8,25,30]

Association between non-alcoholic fatty liver disease and left ventricular diastolic function

Several studies have shown a relationship between NAFLD and LV diastolic dysfunction.[28,31] Simon *et al.*[31] reported more impaired LV diastolic properties in patients with histologically proven NAFLD than those without NAFLD. Lee *et al.*[28] also found that NAFLD patients had larger LV mass index and LA size and elevated LV filling pressure than non-NAFLD patients. In the present study, individuals with NAFLD tended to have higher *E*/e′ ratio (8.8 ± 2.1 vs. 8.4 ± 2.1, $P = 0.071$), but it did not reach statistical significance. This might be partially explained by the fact that *E*/e′ ratio cannot

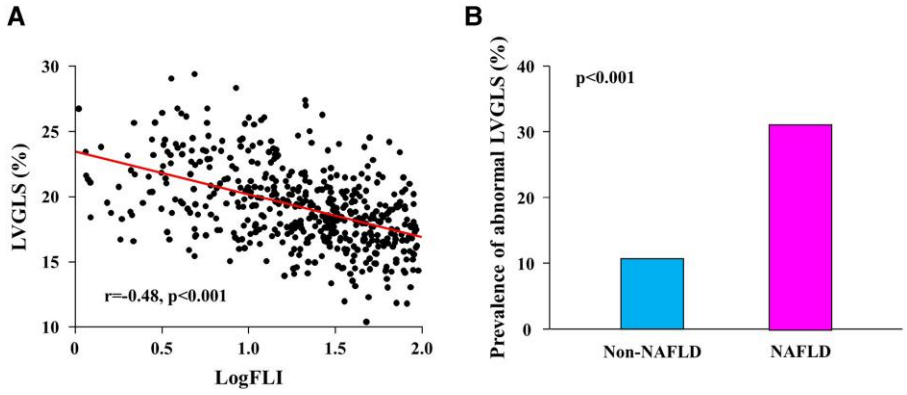


Figure 2 Association between the fatty liver index and left ventricular global longitudinal strain (*A*). The prevalence of abnormal left ventricular global longitudinal strain according to the presence or absence of non-alcoholic fatty liver disease (*B*). FLI, fatty liver index; LVGLS, left ventricular global longitudinal strain; NAFLD, non-alcoholic fatty liver disease.

Table 3 Univariable and multivariable linear regression analysis for left ventricular global longitudinal strain

	Univariable model		Multivariable model	
	Standardized *β* (95% CI)	***P* value**	**Standardized *β* (95% CI)**	***P* value**
Log FLI	−0.48 (−3.85 to −2.77)	<0.001	−0.11 (−1.44 to −0.07)	0.031
Age, years	−0.11 (−0.06 to −0.006)	0.016	−0.08 (−0.05 to 0.0001)	0.051
Men	−0.47 (−1.87 to −1.33)	<0.001	−0.27 (−1.19 to −0.62)	<0.001
Obesity	−0.33 (−1.43 to −0.84)	<0.001	−0.09 (−0.57 to −0.06)	0.014
Hypertension	−0.21 (−1.05 to −0.43)	<0.001	−0.07 (−0.57 to 0.04)	0.093
Diabetes mellitus	−0.23 (−1.85 to −0.84)	<0.001	−0.19 (−1.97 to −0.24)	0.013
Dyslipidaemia	−0.12 (−0.69 to −0.10)	0.009	0.06 (−0.09 to 0.46)	0.185
Current smoking	0.21 (−0.21 to 1.81)	0.116		
Habitual alcohol consumption	−0.19 (−0.89 to −0.32)	<0.001	−0.02 (−0.26 to 0.16)	0.628
RAAS blockers	−0.15 (−1.04 to −0.27)	0.001	0.004 (−0.37 to 0.40)	0.931
Calcium channel blockers	−0.13 (−1.06 to −0.20)	0.004	0.07 (−0.02 to 0.74)	0.067
Statins	−0.18 (−1.07 to −0.36)	<0.001	−0.11 (−0.78 to −0.13)	0.006
Other lipid-lowering drugs	−0.14 (−1.49 to −0.31)	0.003	0.02 (−0.33 to 0.55)	0.618
Oral anti-diabetic agents	−0.20 (−1.80 to −0.69)	<0.001	0.15 (0.06 to 1.80)	0.036
AST, U/L	−0.24 (−0.09 to −0.04)	<0.001	−0.03 (−0.04 to 0.02)	0.604
ALT, U/L	−0.28 (−0.07 to −0.04)	<0.001	−0.008 (−0.03 to 0.02)	0.893
eGFR, mL/min/1.73 m^2	0.11 (0.003 to 0.04)	0.019	−0.03 (−0.02 to 0.007)	0.309
HDL cholesterol, mg/dL	0.27 (0.04 to 0.07)	<0.001	−0.02 (−0.02 to 0.009)	0.518
LDL cholesterol, mg/dL	0.05 (−0.004 to 0.01)	0.246		
HbA1c, %	−0.27 (−2.17 to −1.12)	<0.001	−0.06 (−0.88 to 0.19)	0.203
C-reactive protein, mg/dL	−0.20 (−2.09 to −0.79)	<0.001	−0.004 (−0.49 to 0.43)	0.908
LV end-diastolic diameter, mm	−0.20 (−0.21 to −0.08)	<0.001	0.12 (−0.02 to 0.20)	0.103
LV ejection fraction, %	0.66 (0.33 to 0.41)	<0.001	0.53 (0.26 to 0.33)	<0.001
LV mass index, g/m^2	−0.25 (−0.07 to −0.03)	<0.001	−0.08 (−0.04 to 0.009)	0.214
Relative wall thickness	−0.20 (−16.70 to −6.65)	<0.001	−0.008 (−6.32 to 5.41)	0.878
E/e′ ratio	−0.08 (−0.26 to 0.01)	0.074		
LA volume index, mL/m^2	−0.08 (−0.10 to 0.007)	0.095		

ALT, alanine transaminase; AST, aspartate transaminase; CI, confidence interval; *E*, early diastolic transmitral flow velocity; e′, early diastolic mitral annular velocity; eGFR, estimated glomerular filtration rate; FLI, fatty liver index; HDL, high-density lipoprotein; LA, left atrium; LDL, low-density lipoprotein; LV, left ventricle; RAAS, renin–angiotensin–aldosterone system.

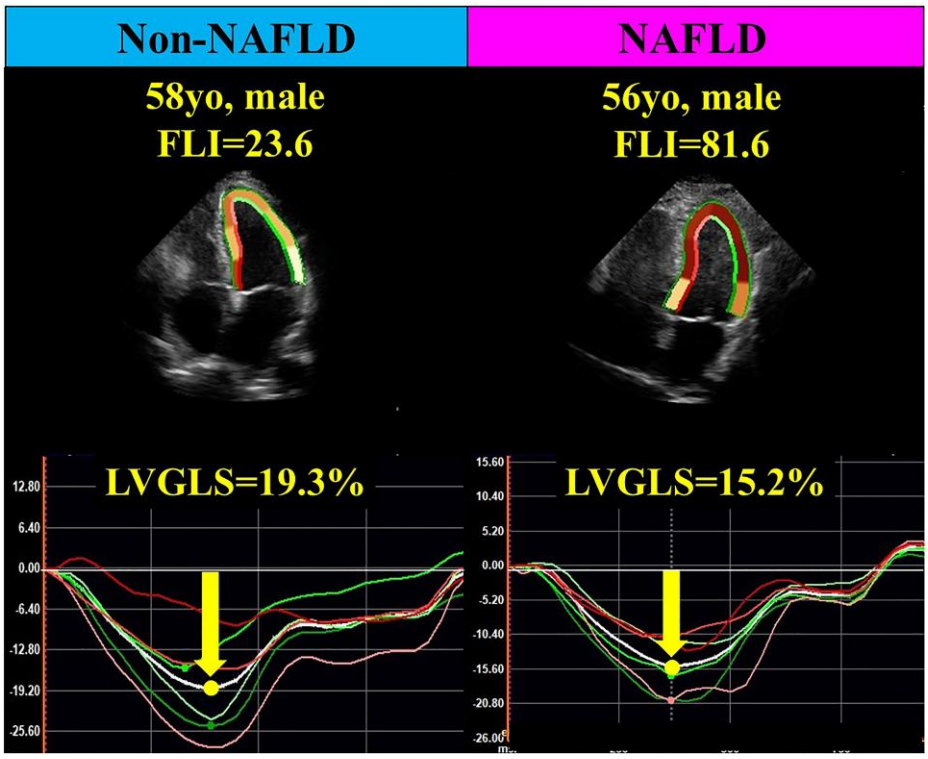


Figure 3 Representative cases with and without non-alcoholic fatty liver disease. The left case without non-alcoholic fatty liver disease (fatty liver index 23.6) had preserved left ventricular global longitudinal strain, while the right case with non-alcoholic fatty liver disease (fatty liver index 81.6) had abnormal left ventricular global longitudinal strain. The arrow indicates the peak left ventricular strain. FLI, fatty liver index; LVGLS, left ventricular global longitudinal strain; NAFLD, non-alcoholic fatty liver disease.

accurately reflect LV filling pressure in the general population with relatively preserved diastolic function.[32] On the other hand, larger LV mass index and relative wall thickness were observed in NAFLD group, which may potentially correspond to LV remodelling in relation to LV diastolic dysfunction.

Clinical implications

The independent association between FLI and subclinical LV systolic abnormalities may explain, at least in part, the increased risk of HF observed in patients with NAFLD. A recent meta-analysis demonstrated that patients with NAFLD had worse LV systolic and diastolic indices than those without NAFLD.[33] Our results extend these previous observations to a subclinical setting. Given the strong predictive value of LVGLS for subsequent HF, evaluation of LVGLS could possibly aid in HF risk stratification in individuals with NAFLD, even in the absence of overt cardiac disease, because approximately one-third of patients with NAFLD had abnormal LVGLS. Recent clinical studies revealed a favourable impact of weight reduction, angiotensin II receptor blockers, and sodium–glucose co-transporter 2 inhibitors on hepatic steatosis.[34–36] Future studies are warranted to investigate whether improvement of NAFLD may ameliorate subclinical LV systolic dysfunction and possibly reduce the risk of HF occurrence.

Limitations

Our study has several limitations. First, the prevalence of NAFLD was lower than the previous studies with ~25%, which may be partly explained by the fact that we included relatively healthy younger population compared with these reports.[9,10] Second, the cross-sectional observational nature of the present study limits the assessment of causality between NAFLD and subclinical LV dysfunction. In addition, we cannot evaluate clinical outcomes in the association of NAFLD with impaired LVGLS, which should be explored in future studies. Third, we evaluated the presence of NAFLD according to the FLI and did not perform ultrasonography and liver biopsy. However, this score was well validated by ultrasonography and biopsy[11,12] and serves as a surrogate measure, allowing for less invasive and more cost-effective treatment, especially in the subclinical setting. Fourth, the information of tricuspid regurgitant velocity was not uniformly available in the present study, and we could not fully address diastolic functional grading according to the current guideline.[20] Finally, we have no data regarding cardiac output and peripheral vascular resistance and could not evaluate a potential impact of haemodynamic condition on LV contractility.

Conclusions

In a general population sample free of overt cardiac and liver disease, the presence of NAFLD was related to subclinical LV systolic impairment. Further investigations are required to explore whether therapeutic interventions for hepatic steatosis may restore myocardial subclinical systolic function and prevent the development of HF.

Lead author biography

Kazutoshi Hirose, MD, PhD, graduated from Chiba University and completed a PhD course in cardiovascular medicine at the University of Tokyo in 2022. He mainly works at the cardiac catheterization laboratory of the University of Tokyo Hospital, and his research focuses on cardiac function, haemodynamic assessment, and the prevention of cardiovascular disease.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

K.H. and K.N. contributed to the conception and design of the work. K.H., K.N., M.R.D.T., N.S., M.H., Ka.K., T.N., M.D., H.M., and I.K. contributed to the acquisition, analysis, and interpretation of data. K.H. drafted the manuscript. K.N., M.R.D.T., S.H., N.S., Y.Y., M.H., Ka.K., Ko.K., T.N., M.D., H.M., M.K., and I.K. critically revised the manuscript. All authors provided final approval and agreed to be accountable for all aspects of the work, ensuring integrity and accuracy.

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