Association of the Non-Alcoholic Fatty Liver Disease Fibrosis Score with subclinical myocardial remodeling in patients with type 2 diabetes: A cross-sectional study in China

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INTRODUCTION
Non-alcoholic fatty liver disease (NAFLD), defined as excessive accumulation of triglycerides (TG) in hepatocytes with no evidence of alcohol abuse or other secondary causes, has become the most prevalent liver disease worldwide1. It represents a spectrum of conditions from simple steatosis to non-alcoholic steatohepatitis, liver fibrosis and cirrhosis, and has been one of the top leading causes for end-stage liver disease and liver transplantation2.
In addition to liver-related complication, a growing body of evidence has shown a close relationship between NAFLD and cardiovascular disease (CVD)\(^{3-5}\). Patients with NAFLD have a higher prevalence of CVD and are more likely to die from CVD than from liver-related death\(^{3-6}\). Among the categories of NAFLD, liver fibrosis is considered as the main indicator of prognosis in NAFLD, and was found to be independently associated with CVD and mortality in different populations\(^{6-9}\). However, the relationship between liver fibrosis and CVD in type 2 diabetes patients, who have a high prevalence of NAFLD, is limitedly investigated\(^{9,10}\).

The NAFLD Fibrosis Score (NFS) is a non-invasive marker widely used to predict advanced fibrosis in patients with NAFLD\(^{11}\). Evidence has shown that the NFS is associated with coronary atherosclerosis, and predicts cardiovascular events and mortality in patients with NAFLD\(^{12,13}\). Further study showed that NFS was also associated with cardiovascular mortality in different populations, including patients with heart failure or coronary artery disease, and even in the general population, regardless of the presence of NAFLD\(^{14,15}\). However, the relationship between the NFS and CVD in type 2 diabetes patients was rarely studied\(^{10,16}\).

In the present study, we carried out a cross-sectional investigation to determine whether the NFS is associated with subclinical myocardial remodeling determined by echocardiography in type 2 diabetes patients.

**METHODS**

**Participants**

All participants were recruited from the Department of Endocrinology and Metabolism in Shanghai General Hospital, Shanghai, China, between May 2017 and June 2019. The diagnosis of type 2 diabetes was defined according to the 1999 World Health Organization criteria. All participants were requested to complete a standardized questionnaire that included questions on the history of present and past illnesses, and medical therapies. Participants with an alcohol intake >140 g/week for men and 70 g/week for women, a history of viral hepatitis, autoimmune hepatitis or other forms of chronic liver disease, a history of heart failure, or renal diseases were excluded from the study. Finally, a total of 1,878 type 2 diabetes patients were included in the final analysis. This study was approved by the institutional review board of Shanghai General Hospital affiliated to Shanghai Jiao Tong University School of Medicine, and carried out in accordance with the principle of the Helsinki Declaration II. Written informed consent was obtained from all participants.

**Anthropometric and biochemical measurements**

All participants were assessed after overnight fasting for at least 8 h. Body weight, height, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by an experienced physician. Body mass index (BMI) was calculated as body weight in kilograms divided by body height squared in meters. Blood samples were collected by one experienced nurse. Fasting serum TG, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine (Scr) and serum uric acid were measured using an autoanalyzer (Beckman, Palo Alto, CA, USA). Blood glucose was measured using the glucose oxidase method. Hemoglobin A1c (HbA1c) was determined by high-performance liquid chromatography.

**Non-invasive markers of liver fibrosis**

The NFS was calculated: $-1.675 + 0.037 \times \text{age (years)} + 0.094 \times \text{BMI (kg/m}^2\text{)} + 1.13 \times \text{impaired fasting glucose/diabetes (yes = 1, no = 0)} + 0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{platelet} \times (\times 10^9/L) - 0.66 \times \text{albumin (g/dL)}$. As all of the participants in the present study had diabetes, NFS = $-1.675 + 0.037 \times \text{age (years)} + 0.094 \times \text{BMI} \times \left(\frac{1.13 + 0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{platelet} \times (\times 10^9/L) - 0.66 \times \text{albumin (g/dL)}}{1.088}\right)$. The participants were first divided into four groups according to the quartiles of NFS (Q1: $-7.23$ to $-1.853$, Q2: $-1.853$ to $-1.088$, Q3: $-1.088$ to $-0.354$, Q4: $-0.354$ to $6.57$). Furthermore, two widely used cut-off points of NFS were selected to categorize the participants into three groups: those with low NFS ($<1.455$), intermediate NFS ($1.455$ to $0.676$) and high NFS ($>0.676$)\(^{17}\).

In addition to the NFS, Fibrosis-4 (FIB-4) and AST to Platelet Ratio Index (APRI), another two non-invasive liver fibrosis scores, were calculated. FIB-4 = age (years) $\times$ AST (U/L) / [-platelet $(\times 10^9/L)$ $\times$ ALT1/2 (U/L)]. APRI = $100 \times$ AST/upper limit of normal range/platelet $(\times 10^9/L)$.

**Echocardiography**

Comprehensive echocardiography, including Doppler and tissue Doppler imaging, was carried out using an Artida cardiac ultrasound scanner (Toshiba Medical Systems, Otawara, Japan) by trained sonographers using a standardized protocol across all field centers. Experienced sonographers made measurements from digitized images using a standard software offline image analysis system (Digisonics, Houston, TX, USA). Indices including left atrial dimension (LAD), interventricular septum thickness (IST), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD) and left ventricular posterior wall thickness (LVPWT) were assessed. LV mass index (LVMI) was calculated with the Devereux corrected formula\(^{19}\). Increased parameters of cardiac dimension were defined as follows: LAD >39 mm (men) or 37 mm (women), IST >10 mm (men) or 9 mm (women), LVEDD >55 mm (men) or 50 mm (women), LVESD >39 mm (men) or 35 mm (women), LVPWT >10 mm (men) or 9 mm (women), LVMI >115 g/m$^2$ (men) or 95 g/m$^2$ (women)\(^{18}\).

**Statistical analysis**

All statistical analyses were carried out using SPSS 13.0 (SPSS, Chicago, IL, USA). Continuous variables are presented as the
mean ± standard deviation or median (interquartile range). Differences among groups were tested by one-way ANOVA for continuous variables and the χ²-test for categorical variables. Pearson’s correlations were carried out to evaluate the associations between NFS and other metabolic risk factors, and to identify the independent factors related to NFS. A multivariate linear regression model was also used to evaluate the independent association of NFS with parameters of subclinical myocardial remodeling. \( P < 0.05 \) was considered statistically significant.

RESULTS
Clinical characteristics of the study population
Among the 1,878 type 2 diabetes patients, 623 were women and 1,255 were men. The clinical and biochemical characteristics of the study population according to the quartiles of NFS are summarized in Table 1. Age, duration of diabetes, BMI, SBP and Scr were significantly increased, whereas DBP, TC, LDL-C, ALT and platelet number were decreased in parallel with the increment of the NFS (all \( P \) for trend values <0.01). No significant difference was found in sex, fasting plasma glucose (FPG), HbA1c, TG, HDL-C and serum uric acid among the four groups.

In addition, the participants were further divided into three groups according to the grades of NFS (low: \(<-1.455\), intermediate: \(-1.455-0.676\), high: \(>0.676\)). As shown in Table 2, compared with participants with low NFS, those with intermediate and high NFS were older and had longer duration of diabetes. BMI, SBP and Scr were significantly increased, whereas DBP, FPG, TG, TC, LDL-C, ALT and platelet number were decreased with the elevation of NFS (all \( P \) for trend values <0.01). No significant difference was found in sex, HbA1c, HDL-C and serum uric acid among the three groups.

Associations between the NFS and metabolic risk factors
Next, the associations between the NFS and other metabolic risk factors were further investigated. Analysis of Pearson’s correlation showed that the NFS was positively associated with age, duration of diabetes, BMI, SBP and Scr, whereas it was negatively associated with DBP, TG, TC, LDL-C, ALT and FPG (Table 3). Multiple stepwise linear regression analysis further showed that sex, age, BMI, LDL-C, ALT, AST and HbA1c were independent determiners of NFS in type 2 diabetes patients (Table 3).

Association of the NFS with subclinical myocardial remodeling
Subclinical myocardial remodeling of the participants was evaluated by echocardiography. Parameters including LAD, IST, LVEDD, LVESD, LVPWT and LVMi were compared among the four groups according to the quartiles of NFS. As shown in

Table 1 | Clinical and biochemical characteristics of the study population according to the quartiles of the Non-Alcoholic Fatty Liver Disease Fibrosis Score

| Variables       | Q1 (−7.23 to −1.853) | Q2 (−1.853 to −0.808) | Q3 (−0.808 to −0.354) | Q4 (−0.354 to 6.57) | P for trend |
|-----------------|----------------------|------------------------|------------------------|---------------------|------------|
| n               | 469                  | 470                    | 470                    | 469                 | 0.916      |
| Male/female     | 315/154              | 330/140                | 299/171                | 311/158             | 0.0001     |
| Age (years)     | 40.9 ± 10.1          | 47.5 ± 10.3            | 52.7 ± 9.3             | 59.8 ± 8.3          | <0.001     |
| Duration (months)| 25 (5–72)           | 37 (3–99)              | 59 (13–120)            | 72 (15–132)         | <0.001     |
| BMI (kg/m²)     | 25.5 ± 3.5           | 25.8 ± 3.6             | 25.6 ± 3.5             | 26.6 ± 4.0          | <0.001     |
| SBP (mmHg)      | 127.3 ± 16.0         | 128.5 ± 16.5           | 129.5 ± 17.9           | 132.6 ± 17.3        | <0.001     |
| DBP (mmHg)      | 78.9 ± 10.0          | 78.4 ± 10.3            | 77.7 ± 10.8            | 76.2 ± 10.2         | <0.001     |
| FPG (mmol/L)    | 87.6 ± 6.8           | 84.9 ± 2.9             | 82.4 ± 2.9             | 80.0 ± 2.9          | 0.102      |
| HbA1c (%)       | 88.8 ± 2.2           | 89.9 ± 2.2             | 87.2 ± 2.1             | 87.2 ± 2.3          | 0.266      |
| TG (mmol/L)     | 1.9 (1.4–2.6)        | 1.6 (1.1–2.5)          | 1.5 (1.0–2.1)          | 1.5 (1.1–2.2)       | 0.0082     |
| TC (mmol/L)     | 5.0 ± 1.3            | 4.9 ± 1.2              | 4.8 ± 1.3              | 4.6 ± 1.5           | <0.001     |
| LDL-C (mmol/L)  | 3.0 ± 0.9            | 2.9 ± 0.9              | 2.9 ± 0.9              | 2.6 ± 0.9           | <0.001     |
| HDL-C (mmol/L)  | 1.0 ± 0.3            | 1.0 ± 0.3              | 1.1 ± 0.3              | 1.0 ± 0.3           | 0.110      |
| ALT (IU/L)      | 29 (20–43)           | 22 (17–33)             | 22 (16–32)             | 18 (13–25)          | <0.001     |
| AST (IU/L)      | 20 (16–27)           | 19 (15–23)             | 19 (16–24)             | 19 (14–26)          | 0.671      |
| Scr (µmol/L)    | 592 ± 19.6           | 603 ± 15.9             | 600 ± 15.7             | 668 ± 26.6          | <0.001     |
| SUA (µmol/L)    | 344 (283–415)        | 320 (268–387)          | 313 (274–368)          | 327 (269–384)       | 0.328      |
| Platelet (10³/µL) | 277 ± 56            | 227 ± 38              | 197 ± 35              | 166 ± 39           | <0.001     |

Continuous variables are presented as means ± standard deviation or median (interquartile range). The participants were divided into four groups (Q1, Q2, Q3 and Q4) according to the quartiles of the Non-Alcoholic Fatty Liver Disease Fibrosis Score: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; Scr, serum creatinine; SUA, serum uric acid; TC, total cholesterol; TG, triglycerides.
Table 2 | Clinical and biochemical characteristics of the study population according to low, intermediate and high Non-Alcoholic Fatty Liver Disease Fibrosis Score

| Variables            | Low NFS (<=1.455) | Intermediate NFS (1.455 to 0.676) | High NFS (>0.676) | P for trend |
|----------------------|-------------------|-------------------------------|------------------|------------|
| n                    | 697               | 1,081                         | 100              |            |
| Male/female          | 216/481           | 369/712                       | 38/62            | 0.223      |
| Age (years)          | 42.8 ± 10.7       | 53.8 ± 9.9                    | 63.1 ± 8.2       | <0.001     |
| Duration (months)    | 34 (5–84)         | 72 (13–132)                   | 120 (27–180)     | <0.001     |
| BMI (kg/m²)          | 25.6 ± 3.5        | 25.8 ± 3.6                    | 280 ± 8.7        | <0.001     |
| SBP (mmHg)           | 127.6 ± 16.1      | 130.5 ± 17.6                  | 131.8 ± 15.7     | <0.001     |
| DBP (mmHg)           | 78.4 ± 10.1       | 77.6 ± 10.4                   | 74.8 ± 11.4      | 0.003      |
| FPG (mmol/L)         | 8.6 ± 5.9         | 8.2 ± 2.9                     | 7.7 ± 2.9        | 0.011      |
| HDL-C (mmol/L)       | 40 ± 12.3         | 42 ± 12.5                     | 39 ± 12.1        | 0.514      |
| TG (mmol/L)          | 1.8 (1.3–2.7)     | 1.6 (1.1–2.3)                 | 1.4 (1.0–2.0)    | 0.018      |
| TC (mmol/L)          | 5.0 ± 1.2         | 4.8 ± 1.3                     | 5.0 ± 1.5        | <0.001     |
| LDL-C (mmol/L)       | 3.0 ± 0.9         | 2.8 ± 0.9                     | 2.4 ± 0.8        | <0.001     |
| ALT (IU/L)           | 10.0 ± 3.0        | 10.0 ± 3.0                    | 10.0 ± 3.0       | 0.781      |
| AST (IU/L)           | 21 (16–29)        | 20 (16–29)                    | 20 (16–29)       | 0.921      |
| Scr (μmol/L)         | 109 (103–115)     | 109 (103–115)                 | 109 (103–115)    | 0.140      |
| Albumin (g/L)        | 39 (37–41)        | 39 (37–41)                    | 39 (37–41)       | 0.223      |
| BMI (kg/m²)          | 25.6 ± 3.5        | 25.8 ± 3.6                    | 280 ± 8.7        | <0.001     |
| SBP (mmHg)           | 127.6 ± 16.1      | 130.5 ± 17.6                  | 131.8 ± 15.7     | <0.001     |
| DBP (mmHg)           | 78.4 ± 10.1       | 77.6 ± 10.4                   | 74.8 ± 11.4      | 0.003      |
| FPG (mmol/L)         | 8.6 ± 5.9         | 8.2 ± 2.9                     | 7.7 ± 2.9        | 0.011      |
| HDL-C (mmol/L)       | 40 ± 12.3         | 42 ± 12.5                     | 39 ± 12.1        | 0.514      |
| TG (mmol/L)          | 1.8 (1.3–2.7)     | 1.6 (1.1–2.3)                 | 1.4 (1.0–2.0)    | 0.018      |
| TC (mmol/L)          | 5.0 ± 1.2         | 4.8 ± 1.3                     | 5.0 ± 1.5        | <0.001     |
| LDL-C (mmol/L)       | 3.0 ± 0.9         | 2.8 ± 0.9                     | 2.4 ± 0.8        | <0.001     |
| ALT (IU/L)           | 10.0 ± 3.0        | 10.0 ± 3.0                    | 10.0 ± 3.0       | 0.781      |
| AST (IU/L)           | 21 (16–29)        | 20 (16–29)                    | 20 (16–29)       | 0.921      |
| Scr (μmol/L)         | 109 (103–115)     | 109 (103–115)                 | 109 (103–115)    | 0.140      |
| Albumin (g/L)        | 39 (37–41)        | 39 (37–41)                    | 39 (37–41)       | 0.223      |

Continuous variables were presented as means ± standard deviation or median (interquartile range). The participants were divided into three groups according to the grades of the Non-Alcoholic Fatty Liver Disease Fibrosis Score (NFS: low, intermediate and high NFS). ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; Scr, serum creatinine; SUA, serum uric acid; TC, total cholesterol; TG, triglycerides.

Table 3 | Associations between the Non-Alcoholic Fatty Liver Disease Fibrosis Score and other metabolic risk factors

| Variables | Univariate | Multivariate |
|-----------|------------|--------------|
|           | r | P       | β | P   |
| Male      | -0.001 | 0.959 | 0.249 | <0.001 |
| Age (years) | 0.596 | <0.001 | 0.064 | <0.001 |
| Duration (months) | 0.297 | <0.001 | - | - |
| BMI (kg/m²) | 0.152 | <0.001 | 0.09 | <0.001 |
| SBP (mmHg) | 0.115 | <0.001 | - | - |
| DBP (mmHg) | -0.08 | <0.001 | - | - |
| TG (mmol/L) | -0.057 | 0.014 | - | - |
| TC (mmol/L) | -0.113 | <0.001 | - | - |
| LDL-C (mmol/L) | -0.15 | <0.001 | -0.122 | <0.001 |
| HDL-C (mmol/L) | 0.21 | 0.37 | - | - |
| FPG (mmol/L) | -0.055 | 0.018 | - | - |
| HbA1c (%) | -0.024 | 0.295 | 0.036 | <0.001 |
| ALT (IU/L) | -0.153 | <0.001 | -0.019 | <0.001 |
| AST (IU/L) | -0.011 | 0.652 | 0.027 | <0.001 |
| Scr (μmol/L) | 0.131 | <0.001 | - | - |
| SUA (μmol/L) | 0.012 | 0.609 | - | - |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; Scr, serum creatinine; SUA, serum uric acid; TC, total cholesterol; TG, triglycerides.

Table 4, LAD, IST, LVEDD, LVESD, LVPWT and LVMI were all gradually increased with the increment of NFS (all P for trend <0.001).

We also compared the aforementioned parameters among the three groups categorized by the grades of the NFS (low, intermediate and high). As shown in Table 5, LAD, IST, LVEDD, LVESD, LVPWT and LVMI were all increased with the increment of NFS (P for trend <0.05). Furthermore, the proportions of increased LAD, IST, LVEDD, LVESD, LVPWT and LVMI were also increased in the group with high NFS.

Linear regression analysis was further carried out to determine the independent association between NFS and echocardiographic parameters. As shown in Table 6, NFS was positively associated with LAD, IST, LVEDD, LVESD, LVPWT and LVMI in univariate analyses (model 1). After adjustment for age, sex, BMI, SBP and DBP (model 2), the NFS remained significantly correlated with the aforementioned echocardiographic parameters. Further adjustment for FPG, HbA1c, TG, TC, HDL-C and LDL-C (model 3) also did not significantly change the associations between NFS and LAD, IST, LVEDD, LVESD, LVPWT and LVMI.

In addition, the associations of FIB-4 and APRI with myocardial remodeling were also assessed. As shown in Table 7, FIB-4 was positively associated with LAD, IST, LVPWT and LVMI. In contrast, APRI was associated with LVPWT only.
Table 4 | Comparison of parameters of myocardial remodeling among groups according to quartiles of the Non-Alcoholic Fatty Liver Disease Fibrosis Score

|                | Q1         | Q2         | Q3         | Q4         | P for trend |
|----------------|------------|------------|------------|------------|-------------|
| LAD (mm)       | 34.3 ± 3.6 | 35.1 ± 3.1 | 35.3 ± 3.7 | 36.7 ± 4.0 | <0.001      |
| IST (mm)       | 8.2 ± 1.0  | 8.3 ± 0.9  | 8.5 ± 1.0  | 8.7 ± 1.0  | <0.001      |
| LVESD (mm)     | 47.7 ± 4.3 | 48.3 ± 4.4 | 48.5 ± 4.0 | 49.2 ± 4.5 | <0.001      |
| LVPWT (mm)     | 31.0 ± 4.0 | 31.4 ± 3.6 | 31.7 ± 3.9 | 32.5 ± 4.9 | <0.001      |
| LVM (g/m²)     | 8.1 ± 0.8  | 8.3 ± 1.6  | 8.4 ± 0.8  | 8.6 ± 0.9  | <0.001      |
|                 | 73.1 ± 14.5| 75.5 ± 17.2| 79.0 ± 15.9| 83.8 ± 17.7| <0.001      |

IST, interventricular septum thickness; LAD, left atrial dimension; LVESD, left ventricular end-systolic diameter; LVM, left ventricular mass index; LVPWT, left ventricular posterior wall thickness.

Table 5 | Comparison of parameters of myocardial remodeling among groups according to grades of the Non-Alcoholic Fatty Liver Disease Fibrosis Score

|                | Low NFS (<−1.455) | Intermediate NFS (−1.455 ~ 0.676) | High NFS (>0.676) | P for trend |
|----------------|------------------|-----------------------------------|-------------------|------------|
| LAD (mm)       | 34.5 ± 3.5       | 35.7 ± 3.7                        | 37.4 ± 4.3        | <0.001     |
| Increased LAD (%) | 3.3%              | 10.6%                             | 32%               | <0.001     |
| IST (mm)       | 8.2 ± 1.0        | 8.5 ± 1.0                         | 8.8 ± 1.1         | <0.001     |
| Increased IST (%) | 1.7%              | 4.6%                              | 8.0%              | <0.001     |
| LVESD (mm)     | 47.8 ± 4.4       | 48.7 ± 4.2                        | 49.4 ± 4.9        | <0.001     |
| Increased LVESD (%) | 2.1%             | 4.3%                              | 8.0%              | 0.009      |
| LVPWT (mm)     | 8.1 ± 0.8        | 8.4 ± 1.2                         | 8.6 ± 1.0         | <0.001     |
| Increased LVPWT (%) | 1%               | 2.7%                              | 4%                | 0.014      |
| LVM (g/m²)     | 73.5 ± 14.2      | 80.1 ± 17.6                       | 84.4 ± 19.5       | <0.001     |
| Increased LVM (%) | 2.6%              | 7.2%                              | 12%               | <0.001     |

IST, interventricular septum thickness; LAD, left atrial dimension; LVESD, left ventricular end-systolic diameter; LVM, left ventricular mass index; LVPWT, left ventricular posterior wall thickness; NFS, Non-Alcoholic Fatty Liver Disease Fibrosis Score.

Table 6 | Association of the Non-Alcoholic Fatty Liver Disease Fibrosis Score with subclinical myocardial remodeling

|                | Model 1 (β, 95% CI) | P       | Model 2 (β, 95% CI) | P       | Model 3 (β, 95% CI) | P       |
|----------------|---------------------|---------|---------------------|---------|---------------------|---------|
| LAD            | 0.83 (0.67, 0.98)   | <0.001  | 0.23 (0.02, 0.44)   | <0.001  | 0.19 (~0.03, 0.40)  | 0.08    |
| IST            | 0.17 (0.13, 0.21)   | <0.001  | 0.10 (0.04, 0.16)   | <0.001  | 0.07 (0.03, 0.15)   | 0.03    |
| LVESD          | 0.55 (0.36, 0.74)   | <0.001  | 0.45 (0.19, 0.71)   | <0.001  | 0.40 (0.09, 0.63)   | <0.01   |
| LVPWT          | 0.52 (0.33, 0.70)   | <0.001  | 0.47 (0.22, 0.73)   | <0.001  | 0.39 (0.14, 0.65)   | <0.01   |
| LVM            | 0.16 (0.12, 0.21)   | <0.001  | 0.12 (0.06, 0.18)   | <0.001  | 0.09 (0.02, 0.15)   | 0.01    |
| LVM            | 3.41 (2.70, 4.12)   | <0.001  | 2.14 (1.23, 3.06)   | <0.001  | 1.97 (1.03, 2.91)   | <0.001  |

Model 1 is unadjusted. Model 2 is adjusted for age, sex, body mass index, systolic blood pressure and diastolic blood pressure. Model 3 is further adjusted for fasting plasma glucose, glycated hemoglobin, triglycerides, total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol. CI, confidence interval; IST, interventricular septum thickness; LAD, left atrial dimension; LVESD, left ventricular end-systolic diameter; LVM, left ventricular mass index; LVPWT, left ventricular posterior wall thickness.

DISCUSSION

NAFLD is closely associated with CVD, while liver fibrosis is the main predictor of CVD and mortality. In the present study, we investigated the association of NFS, a non-invasive marker of liver advanced fibrosis in NAFLD, with subclinical myocardial remodeling in type 2 diabetes patients. It was found that NFS was independently associated with parameters of subclinical myocardial remodeling in patients with diabetes.

The NFS was first used as a marker of advanced fibrosis in patients with NAFLD, however, it was then found to be associated with CVD risk factors in different populations, regardless of the presence of NAFLD or not. Consistently, we also...
observed positive associations of NFS with age, BMI, LDL-C and HbA1c. Furthermore, previous studies showed that NFS was related to CVD and left ventricular diastolic dysfunction in type 2 diabetes patients\textsuperscript{10,16}. In line with the previous studies, we observed an association between the NFS and subclinical cardiovascular remodeling among type 2 diabetes patients in the present study. Altogether, NFS is a promising predictor for myocardial remodeling and CVD in type 2 diabetes patients. In addition, we also investigated the association of other non-invasive liver fibrosis markers with cardiovascular remodeling. Similarly, FIB-4 was also significantly associated with parameters of cardiac remodeling. The present results suggest a close relationship of liver fibrosis and cardiac remodeling in type 2 diabetes patients.

The potential mechanism linking NFS to myocardial remodeling is not fully established. One reason is that the NFS is closely associated with other CVD risk factors, which contribute to the remodeling of the heart. However, if the NFS remained significantly associated with parameters of subclinical myocardial remodeling after adjustment of these risk factors, excluding the possibility that they mediate the association between NFS and myocardial remodeling. Thus, we could assume that there might be other mechanisms involved in the association of NFS with myocardial remodeling. Recently, emerging evidence has shown that the liver talks to the heart by secreting a series of proteins, which are called hepatokines\textsuperscript{21}. Hepatokines, such as FGF21, can act on cardiac myocytes\textsuperscript{22,23}. Abnormal secretion of hepatokines might contribute to the remodeling of the heart in NAFLD. Furthermore, inflammatory factors secreted by liver might also induce cardiovascular remodeling. However, the underlying mechanisms responsible for the remodeling of the heart in NAFLD remain to be determined in future studies.

There were several limitations that require consideration in the present study. First, our study was cross-sectional, which did not allow to make a cause–effect inference. Second, diagnosis of NAFLD was not included in the present study, precluding further analysis by stratifying the presence of NAFLD. However, NFS was previously shown to be associated with CVD and mortality in different populations, regardless of the presence of NAFLD or not\textsuperscript{8,15}. Third, a liver biopsy was not taken in the evaluation of fibrosis. Nevertheless, the NFS is now widely used as a marker of liver advanced fibrosis\textsuperscript{11}.

In conclusion, the present study showed an association between NFS and subclinical myocardial remodeling in type 2 diabetes patients, and it might be helpful for predicting or early detection of myocardial remodeling in diabetes patients.

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DISCLOSURE
The authors declare no conflict of interest.
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