

Prognostic Value of Non-alcoholic Fatty Liver Disease in Predicting Cardiovascular Events in Diabetes Mellitus Patients: A Prospective Cohort Study

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Abstract

Background: Risk stratification of cardiovascular events in patients with type 2 diabetes mellitus (T2DM) has not been established. coronary artery calcium score (CACS) and non-alcoholic fatty liver disease (NAFLD) are independently associated with cardiovascular events in T2DM patients. This study examined the incremental prognostic value of NAFLD assessed by non-enhanced computed tomography (CT) in addition to CACS and Framingham risk score (FRS) on cardiovascular events in T2DM patients.

Methods: This prospective pilot study included 529 T2DM outpatients without history of cardiovascular disease who underwent CACS measurement due to suspected coronary artery disease. NAFLD was defined on CT images as a hepatic: spleen attenuation ratio <1.0. cardiovascular events were defined as cardiovascular death, nonfatal myocardial infarction, late coronary revascularization, nonfatal stroke, or hospitalization for heart failure.

Results: Of 529 patients (61% men, mean age 65 years), NAFLD was identified in 143 (27%). During the median 4.4 years of follow-up, 44 cardiovascular events were documented. In multivariate Cox regression analysis, the presence of NAFLD, CACS and FRS were associated with cardiovascular events with hazard ratios of 5.45 (95% confidential interval [CI]: 2.84–10.45; $p < 0.001$), 1.56 (95% CI: 1.32–1.85; $p < 0.001$), and 1.23 (95% CI: 1.08–1.39; $p = 0.001$), respectively. The global chi-square score for predicting cardiovascular events significantly increased from 27.0 to 49.7 by adding NAFLD to CACS and FRS ($p < 0.001$). The addition of NAFLD to a model including CACS and FRS significantly increased the C-statistic from 0.71 to 0.80 ($p = 0.005$). The net reclassification achieved by adding CACS and FRS was 0.551 ($p < 0.001$).

Conclusions: NAFLD assessed by CT, in addition to CACS and FRS, could be useful in assessing T2DM patients at higher risk of cardiovascular events.

Condensed Abstract

This study examined the incremental prognostic value of non-alcoholic fatty liver disease (NAFLD) on CT in addition to coronary artery calcium score (CACS) on cardiovascular disease risk stratification in diabetes mellitus patients. Of 529 patients, NAFLD was identified in 143 (27%). During the median 4.4 years follow-up, 44 cardiovascular events were documented. The global chi-square score for predicting cardiovascular events significantly increased from 27.0 to 49.7 by adding NAFLD to CACS and Framingham risk score ($p < 0.001$). Thus, NAFLD and CACS combined allows improved selection of diabetes mellites patients at higher risk of cardiovascular events.

Background

The prevalence of type 2 diabetes mellitus (T2DM) has rapidly increased throughout the world [1]. T2DM has been reported to be associated with a twofold to fourfold increase in risk of cardiovascular events compared with non-T2DM subjects [2, 3]. Therefore, the prevention of cardiovascular events in T2DM patients has become a major concern. Although several clinical risk scores for the prediction of

cardiovascular events have been proposed, currently there is no widely used risk stratification for T2DM patients. Previous studies have shown that coronary artery calcium score (CACS) determined by coronary computed tomography (CT) provides additional information on cardiovascular events beyond the commonly used Framingham Risk Score (FRS) in T2DM patients [4, 5]. The 2019 American Heart Association and American College of Cardiology (AHA/ACC) guidelines on the primary prevention of atherosclerotic cardiovascular disease allows the use of CACS in intermediate risk patients if risk level is uncertain [6]. Thus, CACS could be a useful factor to determine cardiovascular events risk in T2DM patients.

There is growing evidence that non-alcoholic fatty liver disease (NAFLD) is associated with cardiovascular events independently of established cardiovascular risk factors [7–9]. NAFLD is a frequent comorbidity of T2DM, and the prevalence of NAFLD is markedly increased in patients with T2DM [10]. There is a complex and bidirectional relationship between NAFLD and T2DM [11]. Recently, we reported the prognostic value of NAFLD assessed by non-enhanced CT in patients with suspected coronary artery disease who underwent coronary CT angiography [12], highlighting the benefits of concomitant assessment of liver fat content during the acquisition of coronary CT angiography to detect patients at higher risk of cardiovascular events.

We therefore hypothesize that the assessment of NAFLD using non-enhanced CT, in addition to CACS and FRS, improves the risk stratification of cardiovascular events in T2DM patients. To test this hypothesis, this study was conducted using a cohort of patients with suspected coronary artery disease who underwent CACS measurement. The aim of this study was to evaluate the prognostic value of NAFLD over CACS and FRS in T2DM patients.

Methods

Study population and data collection

Patient enrollment in this study was shown in Figure 1. This prospective study enrolled 529 Japanese outpatients with T2DM from August 2011 to December 2016. Patients had no history of cardiovascular disease but were referred to our hospital with suspected coronary artery disease. We excluded patients who consumed >20 g of alcohol per day, patients with known liver disease, patients currently using oral corticosteroids or amiodarone, and patients with a coexisting active tumor. All of the patients underwent blood tests, measurement of CACS, and abdominal CT on the same day.

Assessment of coronary calcification

CT imaging was performed using a Somatom Definition Flash scanner (Siemens Medical Solutions, Erlangen, Germany). CACS was measured using the following parameters: 120kV, 150mA, and 3-mm thickness. CACS was calculated using an automated computerized system (Virtual Place, Raijin; AZE Inc., Tokyo, Japan) and the Agatston method, which involved multiplying the area of each calcified plaque by

the density factor determined by a peak pixel intensity within the plaque. The plaque-specific scores for all the slices were added together. The density factor was 1, 2, 3, or 4 for plaques with peak intensities of 130 to 199 Hounsfield Units (HU), 200 to 299 HU, 300 to 399 HU, or ≥ 400 HU, respectively [13]. In addition, patients were divided into three groups by CACS: CACS 0, CACS (1–99) and CACS (≥ 100).

Assessment of visceral adipose tissue and NAFLD

Abdominal non-contrast CT scans were carried out alongside cardiac CT, at the level that contained images of the liver, spleen, and umbilicus. The visceral adipose tissue area was assessed using the semi-automatic segmentation technique at the umbilical level [14]. Hepatic and splenic Hounsfield attenuations were measured using circular regions of interest in the liver and spleen [15]. In the liver, we located regions of interests at two segments (right anterior and right posterior). The ratio of hepatic:spleen attenuation was calculated by using the mean HU measurement of the two right liver lobe regions of interest. In this study, we defined hepatic steatosis as a hepatic:spleen attenuation ratio < 1.0 [16]. NAFLD was finally diagnosed after other causes of hepatic steatosis were ruled out.

Assessment of other risk factors

Hypertension was defined as having a seated blood pressure over 140/90 mmHg or undergoing current treatment with antihypertensive medication. Dyslipidemia was defined as one or more of the following: ≥ 150 mg/dL serum triglyceride, < 40 mg/dL high-density lipoprotein cholesterol, ≥ 140 mg/dL low-density lipoprotein cholesterol, or current treatment with a lipid-lowering drug. Smoking status was defined as currently smoking or not smoking. Obesity was defined as a body mass index ≥ 30 kg/m². FRS was calculated according to the Wilson et al. algorithm to estimate the 10-year risk of a coronary heart disease event [17]. In addition, patients were classified into three groups according to the European Society of Cardiology (ESC) recommendation: very-high risk, high risk, and moderate risk [18].

Outcomes and follow up

The patients were followed up prospectively from the date of CT. Follow-up clinical information was obtained from review of medical records or telephone interviews by attending physicians. The study endpoint was cardiovascular events defined as cardiovascular death, nonfatal myocardial infarction, late coronary revascularization, nonfatal stroke, or hospitalization due to heart failure. The diagnosis of myocardial infarction was made using the criteria of typical acute chest pain and persistent ST-segment elevation or positive cardiac enzymes. Late coronary revascularization was defined as percutaneous coronary intervention or coronary artery bypass grafting as indicated by the treating physician due to stable angina with a newly positive functional test. Patients with scheduled revascularization within 90 days of the CACS measurement were not counted as events. These patients were censored at the time of the first revascularization. Hospitalization for heart failure was defined as any unplanned stay overnight

or longer in a hospital environment, for which the principal reason for admission was heart failure. Nonfatal stroke was defined as a sudden onset nonconvulsive and focal neurological deficit persisting for more than 24 hours.

Statistical analysis

Continuous variables are expressed as mean \pm standard deviation or median with interquartile range. Dichotomous variables are expressed as number and percentage. Differences in continuous variables between the two groups were analyzed by Student's t-test or Mann–Whitney U-test as appropriate. Categorical data were compared by chi-squared analysis. In subsequent analysis, triglyceride data were log-transformed because they did not show a normal distribution. Similarly, because the distribution of the Agatston score data was also highly skewed, CACS was log-transformed after adding 1 to all calcium scores to manage values of 0 ($\log[\text{CACS}+1]$). Kaplan–Meier curves were used to estimate cumulative event rates of cardiovascular events. Differences between time-to-event curves were compared by log-rank test. Annual event rates were calculated by dividing the 4-year Kaplan–Meier event rates by 4 and comparing them. The effect of variables on cardiovascular events was assessed using Cox proportional hazard analysis, and the results were reported as hazard ratios (HR) with 95% confidence intervals (CI). The incremental value of NAFLD was assessed by calculating the global chi-squared test and the receiver operating characteristic (ROC) curve analysis. C-statistics were calculated from the ROC curves and compared using DeLong test. The category-free net reclassification improvement was also calculated. All reported p values were two-sided and $p < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS statistical software (version 24; IBM Corp., Armonk, NY, USA) and the R statistical package (version 3.5.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

The mean age of the study population was 65 years, 324 (61%) patients were men, and median CACS was 63. Overall, 143 (27%) patients had CT evidence of NAFLD. Baseline characteristics of patients with and without NAFLD are shown in Table 1. Patients with NAFLD were younger ($p < 0.001$) and had a greater body mass index ($p < 0.001$) and visceral adipose tissue area ($p < 0.001$), and higher prevalence of dyslipidemia ($p = 0.021$), and obesity ($p < 0.001$) compared with patients without NAFLD. The proportion of very high-risk category patients was greater in patients with NAFLD than that in patients without NAFLD ($p = 0.003$). In addition, patients with NAFLD had higher levels of liver enzymes ($p < 0.001$) and triglycerides ($p < 0.001$), and lower high-density lipoprotein cholesterol levels ($p < 0.001$). Significant differences in CACS were found between the two groups with higher CACS in non-NAFLD patients ($p = 0.002$). The mean dose-length product for abdominal CT was 251 mGy.cm, and the effective dose for each imaging modality was 3.77 mSv, using a conversion coefficient of 0.015.

Table 1
Patient characteristics according to presence or absence of NAFLD.

Variables	NAFLD, n = 143	No NAFLD, n = 386	P value
Age, years	60 ± 12	67 ± 12	< 0.001
Male gender	90 (63)	234 (61)	0.627
Body mass index, kg/m ²	28 ± 4	24 ± 4	< 0.001
Visceral adipose tissue, cm ²	139 ± 55	102 ± 57	< 0.001
Hypertension	108 (76)	265 (69)	0.124
Dyslipidemia	98 (69)	222 (58)	0.021
Current Smoker	40 (28)	86 (22)	0.172
Obesity	36 (25)	32 (8)	< 0.001
β blocker	29 (20)	80 (21)	0.91
Calcium channel blocker	55 (39)	157 (41)	0.645
ACE-I or ARB	80 (56)	192 (50)	0.205
Statin	71 (50)	165 (43)	0.156
Creatinine, mg/dl	0.93 ± 0.91	1.14 ± 1.40	0.046
eGFR, ml/min/1.73 m ²	72 ± 19	64 ± 23	< 0.001
AST, IU/L	29 ± 15	22 ± 13	< 0.001
ALT, IU/L	35 ± 22	22 ± 23	< 0.001
Total cholesterol, mg/dl	183 ± 37	183 ± 35	0.911
LDL cholesterol, mg/dl	108 ± 32	109 ± 30	0.767
HDL cholesterol, mg/dl	49 ± 16	56 ± 16	< 0.001
Triglyceride, mg/dl	150(102, 235)	109(81, 156)	< 0.001
HbA1c, %	7.6 ± 1.6	7.3 ± 1.7	0.076
CACS	30(0, 186)	107 (0, 536)	0.002

Data are presented as mean ± standard deviation, number (%), or median [25th–75th percentile].

NAFLD, non-alcoholic fatty liver disease; ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase ratio; LDL, low-density lipoprotein; HDL-C, high-density lipoprotein; HbA1c, glycated hemoglobin A1c; CACS, coronary artery calcium score; FRS, Framingham Risk Score; ESC, European Society of Cardiology.

Variables	NAFLD, n = 143	No NAFLD, n = 386	P value
CACS category (0–99/≥100)	41/52/50	97/90/199	0.001
FRS	8.6 ± 3.9	8.6 ± 3.8	0.796
ESC very-high risk group	110 (77)	245 (64)	0.003
Data are presented as mean ± standard deviation, number (%), or median [25th–75th percentile].			
NAFLD, non-alcoholic fatty liver disease; ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase ratio; LDL, low-density lipoprotein; HDL-C, high-density lipoprotein; HbA1c, glycated hemoglobin A1c; CACS, coronary artery calcium score; FRS, Framingham Risk Score; ESC, European Society of Cardiology.			

Table 2
Univariate and multivariate predictors of cardiovascular events.

Variables	Univariate		Multivariate	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Age (> 65 years)	1.04(1.01–1.07)	0.010	1.01(0.97–1.05)	0.812
Male, gender	1.64(0.87–3.10)	0.127	2.57(1.04–6.35)	0.040
Hypertension	1.28(0.63–2.60)	0.496	0.75(0.36–1.53)	0.420
Dyslipidemia	1.28(0.69–2.36)	0.439	1.10(0.58–2.10)	0.779
Current Smoker	1.21(0.61–2.39)	0.592	0.71(0.33–1.55)	0.388
Obesity	1.17(0.49–2.76)	0.725	1.47(0.59–3.69)	0.410
β blocker	0.56(0.22–1.43)	0.229		
Calcium channel blocker	1.46(0.82–2.67)	0.189		
ACE-I or ARB	1.20(0.66–2.17)	0.554		
Statin	1.05(0.58–1.90)	0.872		
Visceral adipose tissue (> 100 cm ²)	1.91(1.01–3.60)	0.046		
NAFLD	2.91(1.61–5.25)	< 0.001	5.45(2.84–10.45)	< 0.001
Total cholesterol	1.00(0.99–1.01)	0.934		
LDL cholesterol	1.00(0.99–1.01)	0.944		
HDL cholesterol	0.99(0.96–1.01)	0.151		
Log(triglyceride)	1.48(0.84–2.60)	0.178		
HbA1c	0.93(0.77–1.12)	0.424		
Log(CACS + 1)	1.48(1.27–1.72)	< 0.001	1.56(1.32–1.85)	< 0.001
FRS	1.14(1.05–1.24)	0.002	1.23(1.08–1.39)	0.001
ESC very-high risk group	1.41(0.72–2.73)	0.316		

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; NAFLD, non-alcoholic fatty liver disease; LDL, low-density lipoprotein; HDL-C, high-density lipoprotein; HbA1c, glycated hemoglobin A1c; CACS, coronary artery calcium score; FRS, Framingham Risk Score; ESC, European Society of Cardiology.

Outcome data

Forty-six patients (11 NAFLD, 35 non-NAFLD) with scheduled revascularization within 90 days of the indexed CT were censored at the time of revascularization. During a median follow-up of 4.4 years, 44 cardiovascular events were documented (23 events in NAFLD; 1 cardiovascular death, 5 stroke, 5 myocardial infarction, 10 late revascularization, 2 heart failure, and 21 events in non-NAFLD; 3 stroke, 7 myocardial infarction, 8 late revascularization, 3 heart failure). Kaplan-Meier curves showed the cumulative event free survivals for cardiovascular events in patients stratified by CACS (0, 1–100 or ≥ 100), with or without NAFLD. As shown in Figure 2A, the annual cardiovascular events rate in patients with NAFLD was significantly greater than the event rate in patients without NAFLD (2.95% vs. 0.98%; $p < 0.001$). In addition, patients were divided into 3 groups according CACS and compared by the presence or absence of NAFLD (Figure 2B–D). Patients with NAFLD and CACS ≥ 100 had significantly greater incidence of cardiovascular events. Annual event rates for cardiovascular events in patients with CACS 0 in patients with and without NAFLD were very low and did not differ between two groups (0.00% vs. 0.30%; $p = 0.513$) (Figure 2B). Annual event rates for cardiovascular events in patients with CACS 1–99 and ≥ 100 were significantly greater in NAFLD patients than in non-NAFLD patients (2.25% vs. 0.33%; $p = 0.024$) (Figure 2C) and (6.40% vs. 1.78%; $p < 0.001$) (Figure 2D). In univariate Cox regression analysis, presence of NAFLD, CACS, and FRS were associated with cardiovascular events. In multivariate Cox regression analysis, the presence of NAFLD, CACS, and FRS were associated with cardiovascular events with HR of 5.45 (95% CI: 2.84–10.45; $p < 0.001$), 1.56 (95% CI: 1.32–1.85; $p < 0.001$), and 1.23 (95% CI: 1.08–1.39; $p = 0.001$), respectively.

Comparison of predictive performance for cardiovascular events

We investigated the incremental value of NAFLD compared with CACS and FRS in predicting cardiovascular events. The global chi-square score and ROC curve analysis were calculated to assess the incremental predictive value of NAFLD. As shown in Figure 3A, by adding NAFLD to log (CACS+1) and FRS, the global chi-square score was significantly increased from 27.0 to 49.7 ($p < 0.001$). Figure 3B shows the results of ROC analysis comparing the area under curve for each group. By adding NAFLD, the C-statistic of Model 1 (FRS + log [CACS+1]) was significantly increased from 0.71 to 0.80 ($p = 0.005$). The net reclassification achieved by adding log (CACS+1) and FRS was 0.551 ($p < 0.001$). Thus, the addition of NAFLD to CACS and FRS resulted in an improvement in predictability of cardiovascular events.

Discussion

This study demonstrates that the presence of NAFLD in non-enhanced CT images, in addition to CACS and FRS, improves the risk classification of cardiovascular events in T2DM patients. As this is a study using a cohort of T2DM patients with suspected coronary artery disease, further studies are needed to test whether our results apply to all T2DM patients.

Several lines of evidence show that NAFLD is associated with increased risk of cardiovascular events in T2DM patients. In an observational study of 2103 T2DM patients, NAFLD was associated with increased incidence of cardiovascular disease events after adjustment for multiple risk factors (HR 1.96, 95% CI 1.4–2.7) [19]. The mechanisms by which NAFLD increases cardiovascular events risk are complex and not fully understood. The presence of systemic inflammation promoted by cytokines secreted from the liver is a possible mechanism. Systemic inflammation leads to endothelial dysfunction altering vascular tone and enhancing vascular plaque formation. In NAFLD patients, cytokines are increased with severity of liver disease [20]. This mechanism is also supported by a clinical study which has shown significant association between the stage of liver fibrosis and increased risk of both liver-related and cardiovascular mortality in NAFLD patients [21].

CACS is a well-established surrogate marker of subclinical coronary artery atherosclerotic plaque burden, which can provide a risk prediction beyond the risk score. Budoff et al. reported that CACS is independently and strongly associated with cardiovascular events, and CACS > 100 signifies at least a 7.5% 10-year risk of cardiovascular events regardless of age, gender, or ethnicity in 6814 subjects from the general population. CACS is also used for cardiovascular events risk prediction in T2DM patients, with elevated CACS in T2DM compared with non-T2DM subjects [22]. The Diabetes Heart Study comprising 1123 T2DM patients demonstrated that CACS predicts cardiovascular events more accurately than FRS [4]. Based on this, the 2019 AHA/ACC guidelines on the primary prevention of atherosclerotic cardiovascular disease included the measurement of CACS among patients in intermediate risk groups [6].

NAFLD is reported to be associated with higher and increasing CACS in some studies [23]. However, the association between NAFLD and CACS has not been consistent across all studies, especially in T2DM patients. In a study of 213 participants with T2DM, NAFLD was not associated with CACS in patients with HbA1c < 7%, but was significantly associated with CACS in patients with HbA1c \geq 7% [24]. In contrast, McKimme et al. reported no significant association between hepatic steatosis and CACS in T2DM patients [25]. In addition, Kim et al. reported an association between NAFLD and the prevalence of CACS, but this association was attenuated and is no longer statistically significant after adjusting for insulin resistance [26]. Our study also did not show an association between NAFLD and higher CACS. As our results indicate NAFLD and CACS are independent factors, but the combination of NAFLD and CACS may enable more accurate selection of T2DM patients who are at higher risk of cardiovascular events.

In clinical practice, ultrasonography is commonly used to assess liver fat infiltration; however, non-enhanced CT can be a useful means of diagnosing liver fat. Previous studies have shown that liver:spleen ratio < 1.0 can be used effectively to diagnose the presence of liver fat with high reproducibility [16, 27, 28]. In this study, patients underwent abdominal CT concomitant with coronary CT angiography, which was required to assess coronary artery disease in the patients. Although the association between NAFLD and cardiovascular disease has been established, routine screening for NAFLD in patients is not currently recommended.

Our study has several limitations that need to be addressed. First, the number of patients and cardiovascular events are relatively small. In addition, our results cannot apply directly to the T2DM population or other ethnic groups because our study population consists of only Japanese patients who had suspected coronary artery disease. Second, histological severity of liver damage was not confirmed in this study. However, CT is a useful tool to diagnose NAFLD without the complications of invasive methods. Third, longitudinal information on the change in medications, risk factor control, changes in body mass index, and fluctuations in life style during the follow-up period was not available. Fourth, there is a concern about additional radiation exposure by abdominal CT at the time of measuring CACS.

Conclusion

Our study demonstrates the potential incremental prognostic value of NAFLD assessed by non-enhanced CT, in addition to CACS on cardiovascular events risk stratification in T2DM patients. Further studies are needed to validate whether the examination of NAFLD and CACS in non-enhanced CT is applicable to all T2DM patients.

Abbreviations

CACS: Coronary artery calcium score

CT: Computed tomography

ESC: European Society of Cardiology

FRS: Framingham risk score

HbA1c: Glycated hemoglobin A1c

HU: Hounsfield Units

NAFLD: Non-alcoholic fatty liver disease

ROC: Receiver operating characteristic

T2DM: Type 2 diabetes mellitus

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of Okayama University Hospital and conducted in accordance with the principles contained within the Declaration of Helsinki. All patients enrolled in the study provided written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

We declare that we have no conflict of interest.

Funding

No funding to declare.

Authors' contributions

KI and TM designed the study, analyzed the data, and wrote the manuscript. KO, TM, HT, KE, MY, and KN collected the data. MH and HI assisted in data interpretation and manuscript revision. All authors read and approved the manuscript.

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Figures

Figure 1

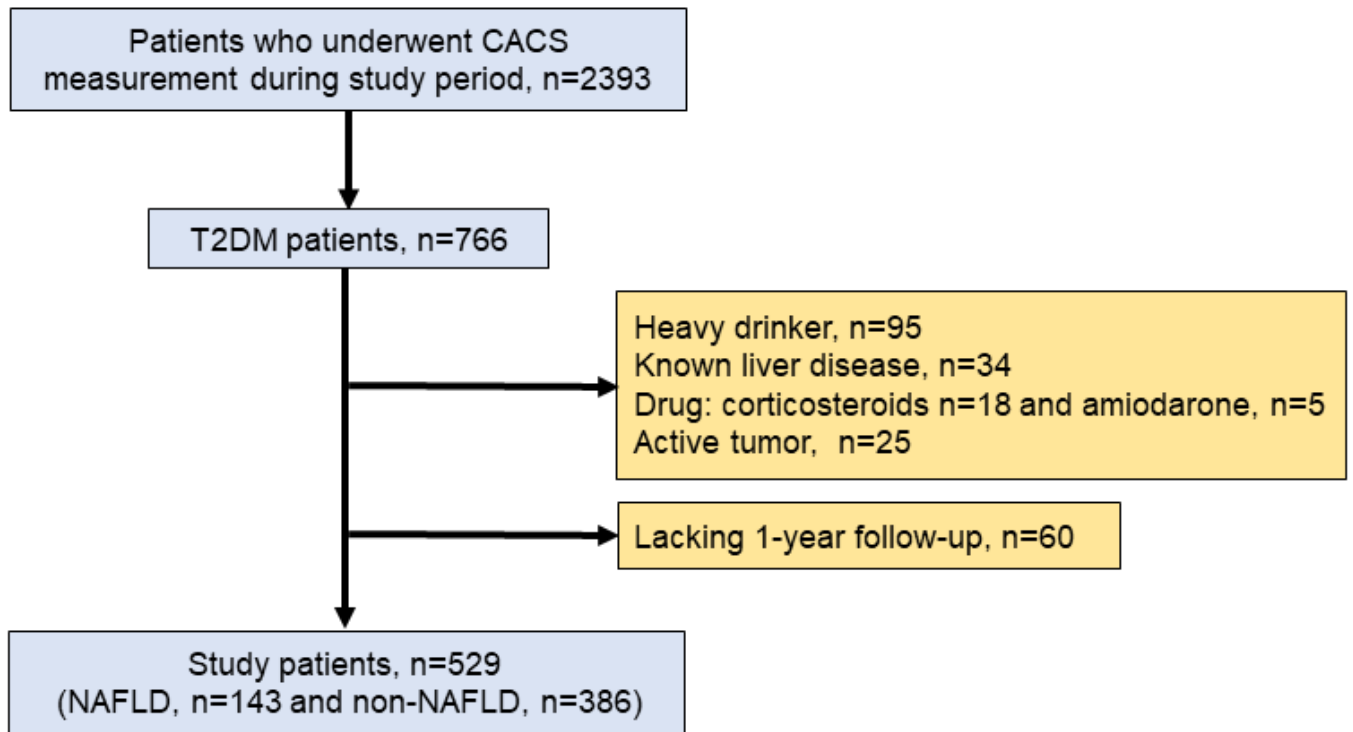


Figure 1

Flowchart showing the study design. CACS, coronary artery calcium score; T2DM, type 2 diabetes mellitus; NAFLD, non-alcoholic fatty liver disease

Figure 2

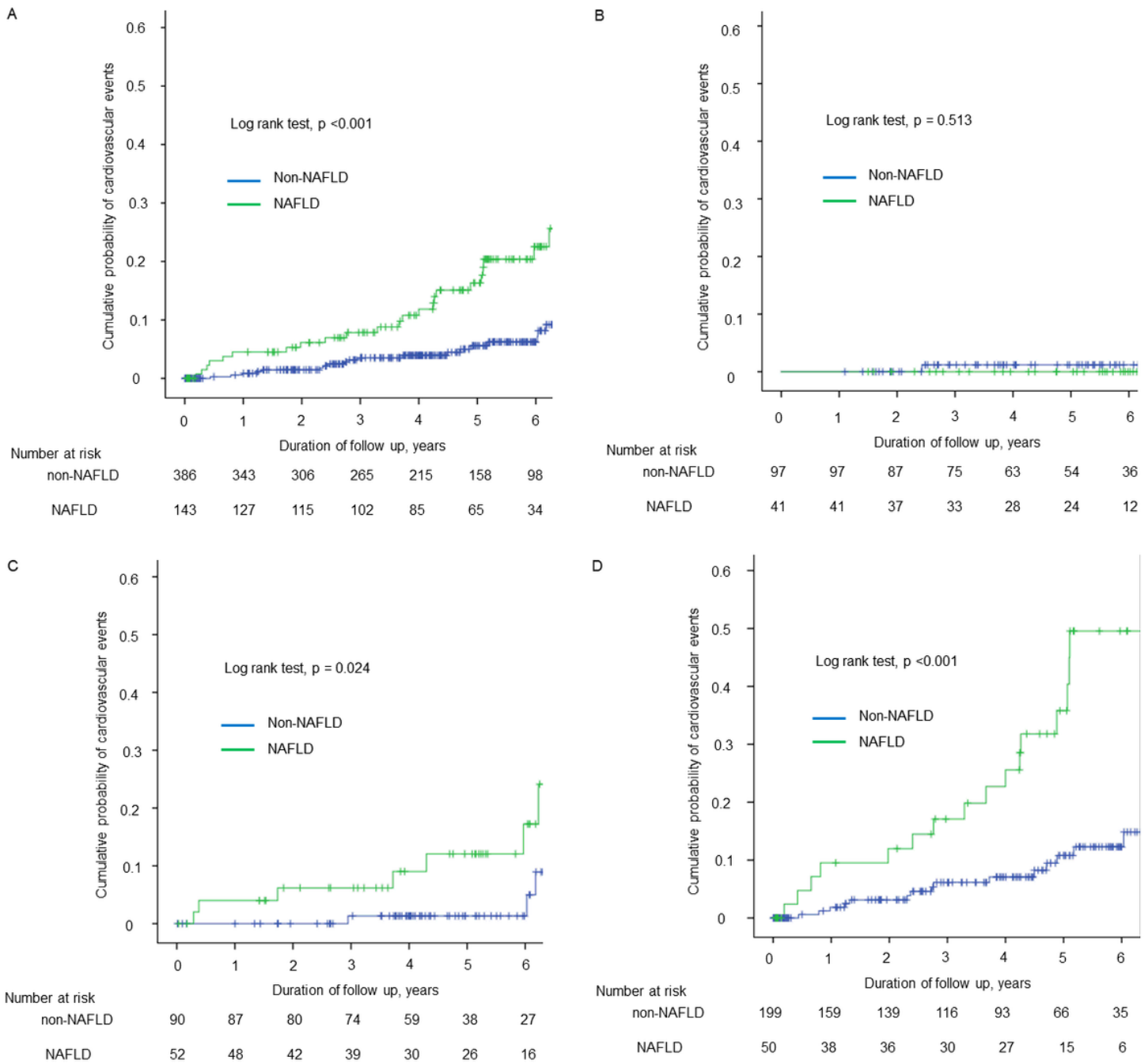


Figure 2

Kaplan–Meier curves showing cumulative incidence of cardiovascular events. Kaplan–Meier curves of cardiovascular events presented according to (A) presence or absence of NAFLD, and (B-D) presence or absence of NAFLD according to CACS categories. CACS, coronary artery calcium score; NAFLD, non-alcoholic fatty liver disease

Figure 3

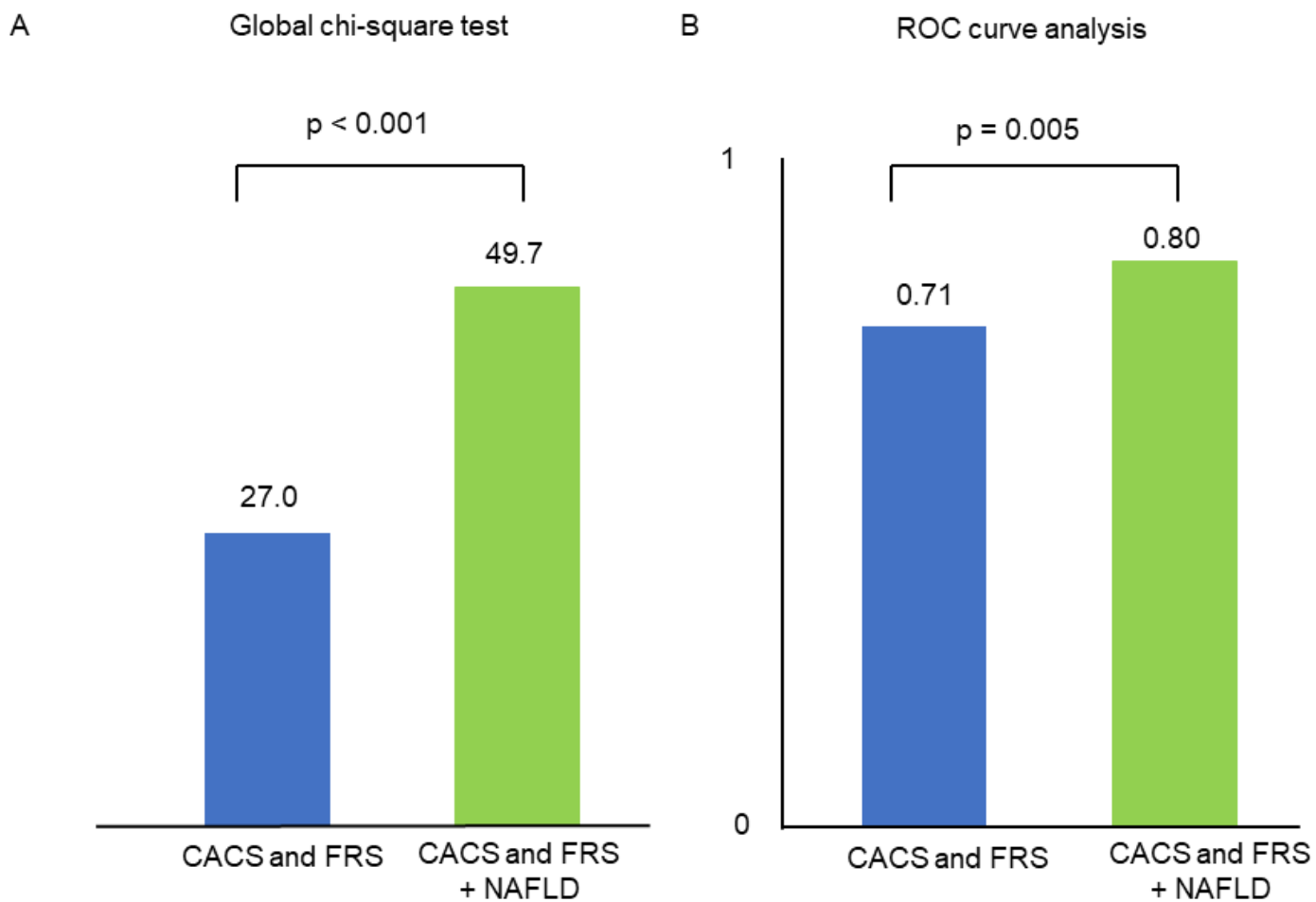


Figure 3

Incremental prognostic value of NAFLD added to CACS and FRS. (A) Global chi-squared test. (B) Receiver operating characteristic curve analysis. NAFLD, non-alcoholic fatty liver disease; CACS, coronary artery calcium score; FRS, Framingham risk score