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Prognostic value of Coronary artery calcium score for the prediction of atherosclerotic cardiovascular disease in participants with suspected nonalcoholic hepatic steatosis: Results from the Multi-Ethnic Study of Atherosclerosis

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Abstract

Background: Nonalcoholic fatty liver disease (NAFLD) is associated with an increased risk of atherosclerotic cardiovascular disease (ASCVD) events; thus, a diagnostic approach to help identify NAFLD patients at high risk is needed. In this study, we hypothesized that coronary artery calcium (CAC) screening could help stratify the risk of ASCVD events in participants with suspected nonalcoholic hepatic steatosis.

Methods: A total of 713 participants with suspected nonalcoholic hepatic steatosis without previous cardiovascular events from the Multi-Ethnic Study of Atherosclerosis (MESA) were followed for the occurrence of incident ASCVD. Nonalcoholic hepatic steatosis was defined using non-enhanced computed tomography and liver/spleen attenuation ratio <1. Cox proportional hazards regression models were used to estimate hazard ratios (HR). C-statistics and areas

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under the time-dependent receiver operating characteristic curves (tAUC) were used to compare incremental contributions of CAC score when added to the clinical risk factors.

Results: In multivariable analyses, CAC score was found to be independently associated with incident ASCVD (HR = 1.33, 95% CI = 1.22–1.44, p < 0.001). The addition of CAC score to clinical risk factors increased the C-statistic from 0.677 to 0.739 (p < 0.001) and tAUC at 10 years from 0.668 to 0.771, respectively. In subgroup analyses, the incremental prognostic value of CAC score was more significant in participants with low/borderline- (<7.5%) and intermediate- (7.5–20%) 10–year ASCVD risk scores.

Conclusions: The inclusion of CAC score in global risk assessment was found to significantly improve the classification of incident ASCVD events in participants with suspected nonalcoholic hepatic steatosis, indicating a potential role for CAC screening in risk assessment.

Introduction

Due to the rising prevalence of obesity and type 2 diabetes, nonalcoholic fatty liver disease (NAFLD) has become the most common liver disease globally. It is a spectrum of disease, ranging from simple steatosis to non-alcoholic steatohepatitis, advanced fibrosis and cirrhosis. In the United States, the prevalence of NAFLD is estimated at 25% and is projected to increase to 33.5% by 2030[1, 2]. More NAFLD patients die from atherosclerotic cardiovascular disease (ASCVD) than liver-related complications, and many studies have identified NAFLD as an independent risk factor for ASCVD events beyond its associated comorbidities [3][4]. As the global prevalence of NAFLD increases and healthcare costs rise, the prevention of ASCVD events in NAFLD patients has become a critical public health concern. The 10–year ASCVD risk score has been widely adopted in clinical practice to estimate risk in adults without ASCVD. Intermediate and high 10–year ASCVD scores (7.5%) can also be used to risk stratify NAFLD patients [5]. While the other recent study has reported the possibility of underestimating the absolute risk in NAFLD patients[6]. Thus, there is an unmet need for data to guide clinicians in risk stratification of NAFLD patients regarding future risk for ASCVD.

Coronary artery calcification (CAC) score determined by non-enhanced computed tomography (CT) is a simple, quick, and easy test that is available to assess the presence and extent of coronary atherosclerosis. It is well established that CAC score is a powerful predictor of ASCVD events in various populations[7]. Furthermore, previous studies have demonstrated that CAC score provided additional information beyond clinical risk scores [8][9]. However, despite the potential for using CAC scores to identify higher risk of ASCVD events among NAFLD patients, there have been no studies to date evaluating the prognostic value of CAC scores in this patient population. As a result, there is currently insufficient evidence to routinely recommend CAC screening for risk stratification in NAFLD patients.

In this study, we sought to evaluate the prognostic value of CAC score in participants with suspected nonalcoholic hepatic steatosis, one of the spectra of NAFLD, by using the multi-ethnic study of atherosclerosis (MESA) cohort. Understanding this topic will allow for a more comprehensive approach of evaluating ASCVD risk in individuals with NAFLD.

Materials and Methods

Study population

We included participants from the Multi-Ethnic Study of Atherosclerosis (MESA), a prospective cohort study of 6814 men and women aged 45 to 84 years without known cardiovascular disease at the time of enrollment. The study enrolled individuals from four race/ethnicity groups (White [38.5%], African American [27.5%], Hispanic [22.1%], and Chinese [11.9%]) at 6 different sites in the United States (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles, California; New York, New York and St. Paul, Minnesota). from July 2000 through August 2002. The study design of MESA has been previously published [10]. All study participants provided written informed consent, and the aggregated data was deidentified. The study was approved by the institutional review board of each site.

Figure 1 shows the flow diagram of the study design. A total of 4389 participants had adequate non-enhanced CT imaging to diagnose hepatic steatosis. Of them, we excluded 226 participants with a history of heavy alcohol use (>14 drinks/week for men and >7 drinks/week for women), known liver disease, or oral corticosteroid or amiodarone use. Additionally, 30 participants were excluded due to missing variables for alcohol use, liver disease, and corticosteroid/amiodarone use. After these exclusions, 4133 participants remained, with 718 participants meeting criteria for suspected nonalcoholic hepatic steatosis. Of these, we excluded 5 participants with a lack of follow-up data. Ultimately, 713 participants with suspected nonalcoholic hepatic steatosis were included in the final analysis. Among these 713 participants, two were missing total cholesterol and high-density lipoprotein (HDL) cholesterol values, three were missing smoking status, and one was missing data on diabetes status.

Assessment of risk factors

As part of the baseline examination, staff at each of the six centers collected information about cardiovascular risk factors. Medical history, anthropometric measurements and laboratory data were collected during the first examination of individuals from the MESA cohort (July 2000 to August 2002). Information about age, gender, ethnicity, and medical history was obtained through questionnaires. Ever smokers were defined as current and former smokers. Current smokers were defined as individuals who smoked cigarettes in the last 30 days, whereas former smokers were defined as individuals who had not smoked in the last 30 days but had smoked 100 cigarettes in their lifetime. Diabetes was defined as fasting glucose of 7.0 mmol/l (126 mg/dl) or use of hypoglycemic drugs. Resting blood pressure was measured by averaging the last 2 of 3 blood pressure measurements used. Total cholesterol, HDL cholesterol and triglyceride levels from blood samples obtained after a 12-h fast were measured at the Collaborative Studies Clinical Laboratory at Fairview-University

Medical Center (Minneapolis, Minnesota). High sensitivity C-reactive protein was measured using a particle enhanced immunonephelometric assay on the BNII nephelometer (Dade-Behring, Inc., Deerfield, Illinois) at the University of Vermont, Burlington, Vermont. The 10-year ASCVD risk score was calculated from the pooled cohort equation [11]. In this study, we classified the study population into three groups based on their risk level: low/borderline (<7.5%), intermediate (7.5–20%), and high-risk (>20%). This classification was based on a prior study [5].

Assessment of nonalcoholic hepatic steatosis

Details of the liver fat measurement within MESA have been previously reported [12]. Baseline cardiac CT scans were utilized to measure hepatic and splenic attenuation values (Hounsfield units) using a region of interest of 100 mm^2. Two regions in the right hepatic lobe and one in the spleen were measured. The liver/spleen attenuation ratio was calculated using the mean of the hepatic measurements divided by the splenic attenuation value. Hepatic steatosis was defined as a liver/spleen attenuation ratio <1. Suspected nonalcoholic hepatic steatosis was defined after exclusion of self-reported secondary causes of liver fat (e.g., alcohol, medications) listed previously.

Assessment of CAC score

CAC score was measured using cardiac-gated electron-beam or multidetector CT, and details of scanning acquisition have been published previously [13]. The CAC scores were measured with either a cardiac-gated electron-beam CT scanner (Chicago, Los Angeles, New York) or a multidetector CT (Baltimore, Forsyth County, St. Paul) at baseline, and adjusted using a standard calcium phantom for calibration. All images were interpreted at the MESA CT reading center (Lundquist Research Institute, Torrance, California). We transformed the CAC score by taking the logarithm of CAC score+1 to maintain the normality of CAC measures. The CAC scores were also categorized as 0, 1–100, and > 100 [14].

Outcome data

Participants were followed from baseline examination (2000–2002) through 2019. They were contacted by telephone every 9–12 months to inquire about interim hospital admissions, cardiovascular outpatient diagnoses, and deaths. To verify self-reported diagnoses, information was collected from death certificates and medical records for all hospitalizations and outpatient cardiovascular diagnoses. Detailed description on follow-up of MESA participants is available online (www.mesa-nhlbi.org). ASCVD events were defined as definite or probable myocardial infarction, definite or probable angina followed by coronary revascularization, definite angina not followed by coronary revascularization, resuscitated cardiac arrest, fatal or non-fatal stroke (not transient ischemic attack), coronary heart disease death, and other cardiovascular death. A detailed description of the adjudication process has been published[10].

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation or median with interquartile range. Dichotomous variables are expressed as numbers (proportion).

Differences in continuous variables between the two groups were analyzed by the paired Student's t-test and the Mann–Whitney U-test as appropriate. Categorical data were compared by chi-squared analysis or Fisher's exact test. Cumulative survival estimates were calculated using the Kaplan-Meier method and compared with the log-rank test. The influence of CAC score on the occurrence of ASCVD was evaluated using the Cox proportional hazard analysis, and the results were reported as the hazard ratio (HR) with 95% confidence interval (CI). The incidence rate was expressed as the number of events per 1,000 patient-years. To determine the independent association between CAC score and ASCVD events, multivariable analysis was performed adjusting for clinical risk factors (age, sex, race/ethnicity, smoking, body mass index, total cholesterol, HDL cholesterol, lipid lowering medication use, hypertensive medication use, systolic blood pressure, and diabetes). By adding CAC score in a baseline model consisting of clinical risk factors, we assessed the ability to predict incident ASCVD by (1) comparing the Harrell's C-statistic (area under the curve [AUC]) of the two nested models and (2) time-dependent receiver-operating characteristic (tROC) analysis. Areas under the tROC curve (tAUC) were reported at 10 years [15]. All reported p values were two-sided and p<0.05 was considered statistically significant. Statistical analyses were performed using the R statistical packages *survivalROC* (version 4.2.1; R Foundation for Statistical Computing, Vienna, Austria).

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Acknowledgements

Results

Baseline characteristics

The mean age of the participants was 61 years old; 47% were men, 35% identified as White, 19% identified as Black, 36% identified as Hispanic, and 10% identified as Chinese American. Table 1 shows the main clinical and laboratory baseline characteristics of the study participants with or without ASCVD events. Participants with ASCVD events were older, more likely to be male, and had higher prevalence of a high 10-year ASCVD score. There were no differences in race/ethnicity, prevalence of diabetes, or use of lipid lowering or hypertensive medications. However, participants with ASCVD events had higher CAC scores.

Association of CAC score and ASCVD events in participants with suspected nonalcoholic hepatic steatosis

During a median follow-up of 17.2 years (IQR: 9.0–18.3 years), 138 ASCVD events (coronary heart disease death [n=10], myocardial infarction [n=28], resuscitated cardiac arrest [n=3], definite angina [n=38], probable angina followed by coronary revascularization [n=4], stroke [n=45], other cardiovascular death [n=10]) were recorded. Figure 2A shows the Kaplan-Meier curves stratified by baseline CAC score. Participants with higher CAC

scores at baseline had a greater event rate (Supplemental Figure). Figure 2B shows the Kaplan-Meier curves stratified by 10-year ASCVD risk. Compared with low/borderline-risk group, intermediate- and high-risk groups were significantly associated with higher event rates. As shown in Table 2, univariate Cox regression analysis identified that log(CACS+1) was significantly associated with ASCVD events (HR, 95% CI 1.38, 1.29–1.48, p < 0.001). Furthermore, multivariable Cox regression analysis identified that log(CACS+1) was independently associated with ASCVD events after adjustment for clinical risk factors (HR, 95% CI 1.33, 1.22–1.44, p < 0.001). By adding log(CACS+1) to clinical risk factors, the Harrell's C-statistic increased from 0.677 to 0.739 (p < 0.001) (Table.3). Adding log(CACS+1) to clinical risk factors improved the tAUC at 10 years from to 0.668 and 0.771. Thus, the discrimination for incident ASCVD was improved when CAC score was added to clinical risk factors.

Association of CAC score and ASCVD events in participants with suspected nonalcoholic hepatic steatosis stratified by 10-year ASCVD risk

The additional predictive value of CAC scores for ASCVD events was further analyzed when participants with suspected nonalcoholic hepatic steatosis were stratified by 10-year ASCVD risk score (low/borderline-risk group [n= 296], intermediate-risk group [n= 258], high-risk group [n= 154]). The number of ASCVD events in each group was 31 (low/borderline-risk group), 57 (intermediate-risk group), and 50 (high-risk group), respectively. As shown in Supplemental Figure and Figure 3A-3C, participants with a CAC score >100 had greater event rates in all groups stratified by 10-year ASCVD risk score. Of note, participants with a CAC score of 0 had very low ASCVD event rates in the low/borderline-risk group, with 2.01 events per 1,000 patient-years; however, those in the intermediate- and high-risk groups had relatively high event rates, with 8.59 events per 1,000 patient-years and 16.98 events per 1,000 patient-years, respectively (Supplemental Figure). Among subjects with a CAC score of 0, there were 6 ASCVD events (coronary heart disease death [n=1], myocardial infarction [n=2], definite angina [n=2], stroke [n=1]) in the low/borderline-risk group ,13 ASCVD events (coronary heart disease death [n=3], myocardial infarction [n=2], stroke [n=8]) in the intermediate-risk group, and 8 ASCVD events (myocardial infarction [n=1], definite angina [n=1], stroke [n=5], other cardiovascular death [n=1]) in the high-risk group, respectively. In multivariable Cox regression analysis, log(CAC score+1) was independently associated with ASCVD events after adjustment for clinical risk factors in all groups (Table 2). By adding log(CAC score+1) to clinical risk factors, the Harrell's C-statistic changed from 0.709 to 0.812 (p=0.023) in the low/borderline-risk group, 0.593 to 0.691 (p=0.009) in the intermediate-risk group, and 0.636 to 0.632 (p=0.540) in the high-risk group (Table 3). By adding log(CAC score+1) to clinical risk factors, the tAUC at 10 years changed from 0.783 to 0.859 in the low/borderline-risk group, 0.574 to 0.721 in the intermediate-risk group, and 0.635 to 0.664 in the high-risk group. Thus, improvements in event prediction by addition of CAC score were more significant in the low/borderline- and intermediate-risk participants.

Discussion

To our knowledge, this is the first study to investigate the prognostic value of CAC score in participants with suspected nonalcoholic hepatic steatosis. Three main findings emerged from our study. Firstly, CAC scores were found to be an independent predictor of incident ASCVD events in participants with suspected nonalcoholic hepatic steatosis. Secondly, participants with CAC score of 0 had very low ASCVD event rates in the low/borderline-risk score group, while those in intermediate- and high-risk score groups had relatively high event rates. Thirdly, including CAC scores in addition to clinical risk factors significantly improved the ability to predict incident ASCVD events, with the greatest improvement seen in the low/borderline- and intermediate- risk score groups.

A strong association between NAFLD and increased risk of ASCVD events and mortality has already been established [4, 16], and there is an unmet need for a diagnostic approach to identify individuals with NAFLD who are at higher risk and would benefit from prevention therapy. Measuring CAC score has been shown to have strong prognostic value for ASCVD events in various populations, including type 2 diabetes individuals [17], a group of patients where NAFLD is extremely prevalent [18]. Although several cross-sectional studies have found an independent associations between NAFLD and the presence of CAC[19, 20], there have been no longitudinal studies showing the role of CAC score in assessing ASCVD risk in individuals with NAFLD. In this context, our study demonstrated the value of CAC screening in identifying individuals with suspected nonalcoholic hepatic steatosis, one of the spectra of NAFLD, at higher risk for ASCVD events. These results suggest that measuring CAC score may be helpful in determining the appropriate strategy for preventive therapies. CAC has also been reported to have potential benefits for patient behavior [7]. Recent data showed the rate of ASCVD events in NAFLD patients dramatically decrease by increasing the proportion of adequately treated risk factors [21]. We believe CAC measurement in this population also helps to improve patient lifestyle, risk factor control, and medication adherence, leading to improvement of their prognosis.

A CAC score of 0 has been established as a powerful negative risk marker for ASCVD events over a 10–15 period [22, 23]. According to current guidelines, intermediate-risk individuals with a CAC score of 0 can avoid statin therapy [24]. However, our study demonstrated that participants with a CAC score of 0, particularly those in the intermediate- and high-risk categories, had relatively higher event rates. Our results suggest that using a CAC score of 0 to downgrade estimated risk is not appropriate for individuals with suspected nonalcoholic hepatic steatosis, as with other conditions such as diabetes, strong family history of premature coronary heart disease, and current smoking. The mechanisms involved in higher risk despite a CAC score of 0 in participants with suspected nonalcoholic hepatic steatosis are partly explained by the association between nonalcoholic hepatic steatosis and plaque progression. Nonalcoholic hepatic steatosis has been reported as an independent predictor of CAC progression[25], indicating that the presence of nonalcoholic hepatic steatosis may promote the conversion from a CAC score of 0 to a CAC score greater than 0. However, it should be noted that this claim is based on the observational nature of this study, and future research is needed to confirm this relationship.

The recent study by Golabi et al. showed that patients with NAFLD who have an elevated ASCVD risk score 7.5% have a higher risk of cardiovascular mortality, confirming the usefulness of such scoring systems in identifying patients at risk in this population[5]. On the other hand, Henson et al. recently found that the scoring system used in their study may underestimate absolute risk in NAFLD patients [6]. In our study, we also observed that CAC score had incremental prognostic value in participants with a lower 10-year ASCVD risk ($< 7.5\%$), demonstrating the complementary role of CAC score in participants with suspected nonalcoholic hepatic steatosis. Some previous studies have also shown that CAC screening in lower risk individuals leads to efficient risk stratification. Kavousi et al. in their meta-analysis of CAC screening in women with 10-year ASCVD risk <7.5% found an increase in incident ASCVD for those with any CAC score compared to those with a score of 0 [26]. Participants with suspected nonalcoholic hepatic steatosis tend to be younger when compared to those without suspected nonalcoholic hepatic steatosis in the previous MESA study [20]. Since 10-year ASCVD risk is heavily driven by age, these individuals may be estimated to have lower risk despite the presence of risk factors and an elevated lifetime risk of ASCVD[27]. Our results recommend the use of CAC screening in individuals with suspected nonalcoholic hepatic steatosis, even if they are estimated to be at lower risk.

NAFLD ranges from simple steatosis to non-alcoholic steatohepatitis, advanced fibrosis, and cirrhosis. Many studies have demonstrated that histological severity of fibrosis is strongly associated with ASCVD events and total mortality in patients with NAFLD [28,29]. These findings were supported by previous reports that circulating levels of inflammatory cytokines, well-established biomarkers of atherosclerotic plaque development, rise in tandem with the histological severity of NAFLD [30,31]. In addition, serum-based fibrosis markers such as the NAFLD fibrosis score and fibrosis-4 score reportedly are also associated with an increased risk of ASCVD events [32,33,34]. Unfortunately, the data on liver histological severity and serum fibrosis markers was not available in this study. Future studies combining histological data and CAC scores should explore the incremental value of CAC score over histological data. Furthermore, we have to highlight that our study consisted of subjects with suspected nonalcoholic hepatic steatosis, one of the spectra of NAFLD. To generalize our findings, our results should be confirmed in study subjects including all spectra of NAFLD.

Study Limitations

This study had some limitations. First, the number of study subjects was relatively small. In addition, although MESA is a large population-based cohort, it was not designed to consider hepatic steatosis as its primary objective. Therefore, we cannot deny that selection bias may have affected our findings. Future prospective clinical studies assessing the prognostic value of CAC score in subjects with nonalcoholic steatosis are needed to confirm our findings. Second, hepatic steatosis was diagnosed using CT, which has limited specificity compared to histology or magnetic resonance imaging[35]. Third, liver histological severity was not available in this study. However, CT is still a useful tool for diagnosing hepatic steatosis without the complications associated with more invasive methods. Fourth, our study subjects consisted of participants with suspected nonalcoholic hepatic steatosis. NAFLD has a spectrum ranging from simple steatosis to advanced fibrosis and cirrhosis. Thus, our results cannot be generalized to other NAFLD patients. In addition, our risk estimates only pertain

to the population studied and may not be generalizable to other populations. Finally, liver-related outcomes were not counted as clinical events in this study. Nonalcoholic hepatic steatosis has also been strongly linked to the development of liver-related outcomes and death, especially in long-term observation[36]. Thus, our event definition may have affected our findings.

Conclusions

CAC scoring improved a discriminative ability for predicting ASCVD events in participants with suspected nonalcoholic hepatic steatosis which was better than clinical risk factors alone. This suggests routine CAC screening can be useful in assessing the risk of future ASCVD events in these individuals. However, a CAC score of 0 was associated with relatively high event rates in intermediate- and high-risk score groups, indicating that caution should be exercised when using CAC scores to lower estimated risk. Further investigation is needed to explore the therapeutic implications of CAC screening in individuals with suspected nonalcoholic hepatic steatosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding

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Highlights

- CAC predicted ASCVD in participants with suspected nonalcoholic hepatic steatosis.

- CAC score 0 had relatively high event rates in intermediate/high-risk score groups.

- CAC scores improved the discriminative ability for future ASCVD events.

- CAC screening can be useful to predict ASCVD risk in this population.

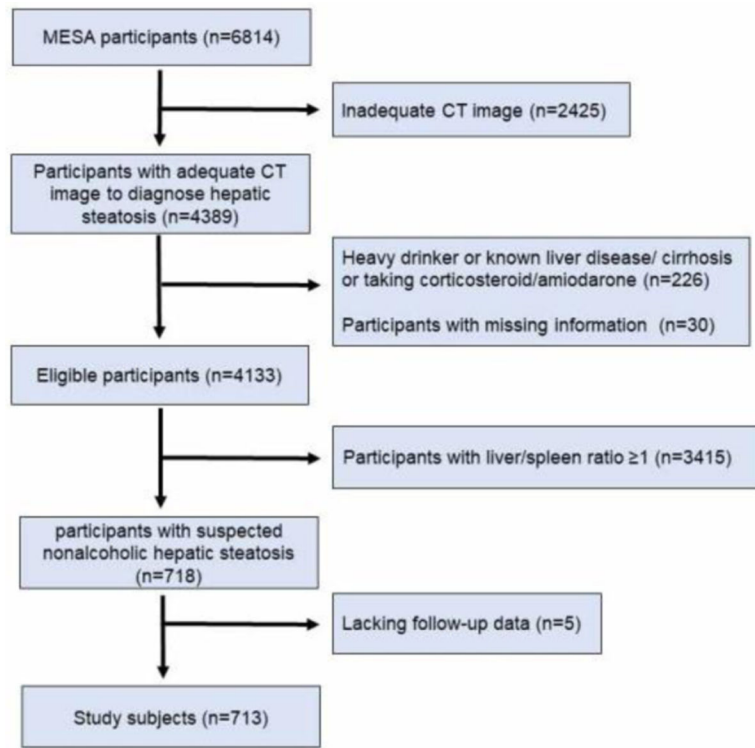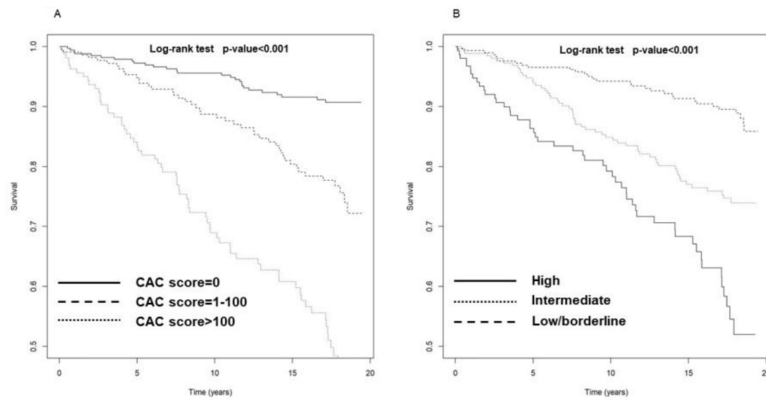**Figure 1.**
Flowchart showing the study design.

Figure 2.
Kaplan-Meier analyses of event-free survival for ASCVD stratified by (A) CAC score or (B) 10-year ASCVD score

ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium.

(A) Low/borderline

(B) Intermediate
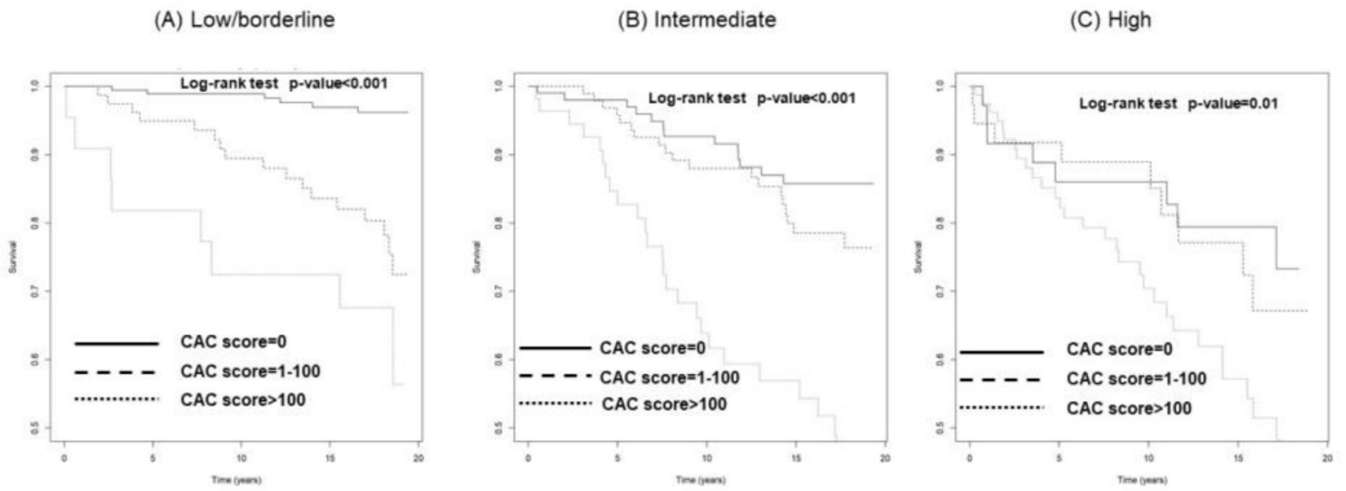
(C) High

Figure 3.

Impact of CAC score on ASCVD in participants with suspected nonalcoholic hepatic steatosis stratified by 10-year ASCVD risk.

Participants were classified according to the following categories: 10-year ASCVD score (A) low/borderline (<7.5%), (B) intermediate (7.5–20%), (C) high (>20%).

ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium.

Table 1

Baseline clinical and laboratory characteristics of the study population

	All n=713	ASCVD (+) n=138	ASCVD (−) n=575	p-value[*]
Age, years	60.9±9.6	64.6±9.0	60.1±9.5	<0.001
Male sex, n (%)	332 (47)	78 (57)	254 (44)	0.012
Body mass index, kg/m^2	31.2±5.4	30.7±4.8	31.3±5.5	0.266
Race/ethnicity				0.899
White, n (%)	251 (35)	52 (38)	199 (35)	
Chinese American, n (%)	72 (10)	14 (10)	58 (10)	
Black, n (%)	136 (19)	24 (17)	112 (19)	
Hispanic, n (%)	254 (36)	48 (35)	206 (36)	
Diabetes, n (%)	154 (22)	37 (27)	117 (20)	0.123
Ever smoker, n (%)	330 (46)	71 (51)	259 (45)	0.208
Lipid lowering medications, n (%)	124 (17)	30 (22)	94 (16)	0.169
Hypertensive medications, n (%)	317 (44)	71 (51)	246 (43)	0.081
Total cholesterol, mg/dl	195±39	191±35	196±40	0.121
HDL cholesterol, mg/dl	45±12	44±14	46±12	0.388
High sensitivity C-reactive protein, mg/l	3.2 [1.4, 6.5]	3.0 [1.3, 6.2]	3.2 [1.5, 6.6]	0.529
Systolic blood pressure, mmHg	127±21	133±21	129±21	0.046
10-year ASCVD Risk				<0.001
Low/borderline -risk, n (%)	296 (42)	31 (22)	265 (46)	
Intermediate-risk, n (%)	258 (36)	57 (41)	201 (35)	
High-risk, n (%)	154 (22)	50 (36)	104 (18)	
CAC score, HU	3.0 [0, 77.2]	86.8 [7.6, 299.3]	0 [0, 36.8]	<0.001
CAC category				<0.001
0, n (%)	333 (47)	27 (20)	306 (53)	
1–100, n (%)	219 (31)	45 (33)	174 (30)	
>100, n (%)	161 (23)	66 (48)	95 (17)	

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

[*] Comparison between ASCVD (+) and ASCVD (−)

ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; HDL, high-density lipoprotein; HU, Hounsfield U.

Table 2

The association between CAC score and atherosclerotic cardiovascular disease events

	Log (CAC score+1)			
	Univariate		Multivariable[*]	
	HR (95% CI)	p value	HR (95% CI)	p value
All participants	1.38 (1.29–1.48)	<0.001	1.33 (1.22–1.44)	<0.001
Subgroup				
Low/borderline-risk	1.60 (1.38–1.86)	<0.001	1.63 (1.34–1.98)	<0.001
Intermediate-risk	1.32 (1.18–1.49)	<0.001	1.35 (1.19–1.54)	<0.001
High-risk	1.15 (1.02–1.28)	0.017	1.19 (1.04–1.36)	0.011

CAC, coronary artery calcium; CI, confidential interval; HR, hazard ratio.

[*] Multivariable models are adjusted for age, sex, race/ethnicity, smoking, body mass index, total cholesterol, high-density lipoprotein cholesterol, lipid lowering medication use, hypertensive medication use, systolic blood pressure, and diabetes.

Table 3

Discrimination improvement for ASCVD prediction with the addition of CAC score to clinical risk factors

	Harrell's C-statistic			Time-dependent area under curve	
	Model 1[*]	Model 1+ Log(CAC score+1)	p value	Model 1[*]	Model 1+ Log(CAC score+1)
All participants	0.677	0.739	<0.001	0.668	0.771
Subgroup Low/borderline-risk	0.709	0.812	0.023	0.783	0.859
Intermediate-risk	0.593	0.691	0.009	0.574	0.721
High-risk	0.636	0.632	0.540	0.635	0.664

CAC, coronary artery calcium.

[*] Model 1 includes age, sex, race/ethnicity, smoking, body mass index, total cholesterol, high-density lipoprotein cholesterol, lipid lowering medication use, hypertensive medication use, systolic blood pressure, and diabetes.