ESC European Society of Cardiology

European Journal of Preventive Cardiology (2021) **28**, 2059–2066
doi:10.1093/eurjpc/zwab120

FULL RESEARCH PAPER

Incremental prognostic value of non-alcoholic fatty liver disease over coronary computed tomography angiography findings in patients with suspected coronary artery disease

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Received 22 January 2021; accepted 23 June 2021online publish-ahead-of-print 19 July 2021

Aims This study aimed to investigate additional risk stratification benefits of hepatic steatosis (HS) concurrently assessed during coronary computed tomography angiography (CTA) in a large patient cohort with suspected stable coronary artery disease (CAD).

Methods and results In this prospective study, 1148 Japanese outpatients without a history of CAD who underwent coronary CTA for suspected stable CAD (mean age 64 ± 14 years) were included. HS, defined on CT as a hepatic-to-spleen attenuation ratio of <1.0, was examined just before the evaluation of adverse CTA findings, defined as obstructive and/or high-risk plaque. The major adverse cardiac events (MACE) were the composite of cardiac death, acute coronary syndrome, and late revascularization. The incremental predictive value of HS was evaluated using the global χ^2 test and C-statistic. HS was identified in 247 (22%) patients. During a median follow-up of 3.9 years, MACE was observed in 40 (3.5%) patients. HS was significantly associated with MACE in a model that included adverse CTA findings (hazard ratio 4.01, 95% confidence interval 2.12–7.59, $P < 0.001$). By adding HS to the Framingham risk score and adverse CTA findings, the global χ^2 score and C-statistic significantly increased from 29.0 to 49.5 ($P < 0.001$) and 0.74 to 0.81 ($P = 0.026$), respectively. In subgroup analyses in patients with diabetes mellitus and metabolic syndrome, HS had significant additive predictive value for MACE over the Framingham risk score and adverse CTA findings.

Conclusion In patients with suspected stable CAD, concurrent evaluation of HS during coronary CTA enables more accurate detection of patients at higher risk of MACE.

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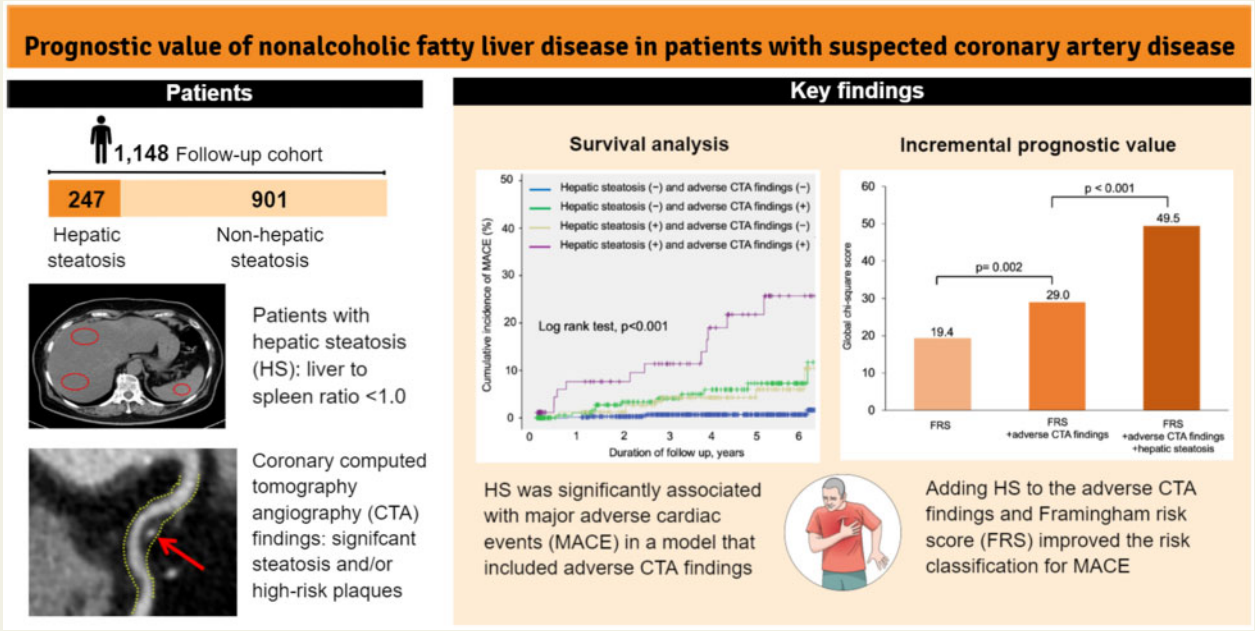
Graphical Abstract



Keywords Coronary artery disease • Computed tomography angiography • Atherosclerotic plaque • Risk assessment • Hepatic steatosis

Introduction

Despite a relative reduction in cardiovascular mortality in the recent decade, accurate risk stratification for patients at a higher risk of future cardiovascular events who would benefit from effective intervention remains of great importance to public health.[1] Coronary computed tomography angiography (CTA) has been established as an accurate diagnostic measure to assess obstructive and non-obstructive plaque characteristics.[2–5] Many studies have demonstrated the prognostic value of the presence of adverse coronary CTA findings, defined as obstructive or high-risk plaques, in patients with suspected coronary artery disease (CAD); especially in comparison to functional testing and clinical risk scores, such as the Framingham risk score (FRS).[6–8] Therefore, coronary CTA is used to guide cardiovascular risk stratification and clinical decision-making.

Emerging evidence has shown that non-alcoholic liver disease is a significant factor associated with the increased risk of cardiovascular events, independently of traditional cardiovascular risks.[9–11] In clinical practice, although ultrasonography and magnetic resonance imaging are widely used to diagnose fatty infiltration, CT usefulness as a measure of hepatic fat has also been reported.[12] We have demonstrated that hepatic steatosis (HS) on non-enhanced CT is significantly associated with the presence of high-risk plaques on coronary CTA, as well as future cardiovascular events, independently of coronary CTA findings in small cohorts of patients with suspected stable CAD.[13,14] In addition, as patients with HS often have metabolic co-morbidities, such as diabetes mellitus and metabolic syndrome, the value of HS in predicting cardiovascular disease over coronary CTA remains unclear.

The aim of this study was to clarify additional risk stratification benefits of HS concurrently assessed during coronary CTA in patients with suspected stable CAD in a large cohort. Furthermore, we investigated the additional predictive value of HS during coronary CTA for cardiovascular events in a patient cohort with diabetes mellitus or metabolic syndrome.

Methods

Study population

This was a prospective, single-centre, cohort study that evaluated the impact of HS on CAD and its prognosis. The study protocol was approved by the institutional review board of the institution where this study was conducted. Additionally, the study was conducted in accordance with the principles of the Declaration of Helsinki. All enrolled patients provided written informed consent. *Figure 1* shows the flow diagram of the study design. Of 1596 Japanese outpatients without a history of CAD who underwent coronary CTA for suspected stable CAD from August 2011 to December 2016, the following were excluded: those who consumed >20 g of alcohol per day,[15] with known liver disease, who were currently using oral corticosteroids or amiodarone, with a coexisting active

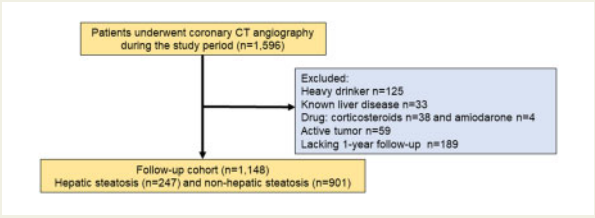


Figure 1 Flowchart showing the study design.

tumour, and with <1 year of follow-up. Thus, the analysis dataset comprised 1148 patients. Of these, 171 patients (15%) had chest pain and the remaining 977 patients (85%) had no symptom but suspected CAD due to other test abnormalities, such as electrocardiogram or stress electrocardiogram. No patients had undertaken any prior single-photon emission computed tomography myocardial perfusion scintigraphy or positron emission tomography for assessment of coronary flow reserve. At baseline, standardized questionnaires were used to collect information about alcohol use, medical history, medication use, and smoking status. Of the 1148 patients that participated in the study, 573 had also been included in our previous study.[13]

Outcome data

A follow-up information was obtained from a review of medical records or telephone interviews blinded to CT results. Major adverse cardiac events (MACE) were defined as the composite of cardiac death, acute coronary syndrome, and late coronary revascularization. Each outcome was reviewed by clinical events review members (K.E. and M.Y.) blinded to CT results according to the relevant criteria. The details of event definitions are provided in the Supplementary material online. Cardiac death was defined as death due to any of the following causes: acute coronary syndrome, heart failure, arrhythmic death, and unclear causes of death in which a cardiac origins could not be excluded. Acute coronary syndrome included myocardial infarction and unstable angina. Late coronary revascularization was defined as planned percutaneous coronary intervention or coronary artery bypass grafting due to stable CAD with a newly positive functional test for ischaemia at more than 90 days after coronary CTA. MACE that occurred in patients with revascularization scheduled within 90 days on indexed coronary CT findings were not included; to eliminate confounding, these patients were censored at the time of first revascularization.

Assessment of risk factors

Detailed definitions of risk factors have been previously described.[16] Metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III.[17] The FRS was used to classify the study population into low- (<10%), intermediate- (10–20%), and high-risk (>20%) groups.[18] The high-risk group was defined as having a high FRS. As a liver fibrosis marker, fibrosis-4 index was calculated as follows: age (years) × AST (U/L)/[ALT (U/L)$^{1/2}$ × platelet count (10^9/L)].[19]

CT assessment of HS

CT images were acquired with a Somatom Definition Flash scanner (Siemens Medical Solutions, Munich, Germany) as described previously.[14] An abdominal non-contrast CT scan was performed just before the cardiac scan on the same day. A topogram was acquired to define the precise scan range that contained images of the liver and spleen. The scan range was 20 cm, and other scan parameters were as follows: 120 kVp, 250 mAs, and 5-mm slice thickness. We used the same method of assessing HS as previous reports on the Multi-Ethnic Study of Atherosclerosis.[20] Hepatic and splenic Hounsfield attenuations were measured in the largest possible regions.[21] The regions of interest >100 mm^2 included two areas that were aligned with the anterior-posterior dimension of the right liver lobe and one that was aligned with the spleen. In the liver, we located regions of interest by avoiding the inclusion of any large vessels or biliary structures. A hepatic-to-spleen attenuation ratio of <1.0 was defined as the cut-off for a positive diagnosis of HS.[12–14] Visceral adipose tissue area at the level of the umbilicus was assessed using the semi-automatic segmentation technique.[22]

Coronary CT image acquisition and analyses

Coronary CTA images were acquired as previously described.[14] Coronary CTA findings were interpreted by two experienced cardiovascular imagers (K.O. and T.M.) who were blinded to other clinical and abdominal CT data. Plaque characteristics were defined according to the coronary artery disease—reporting and data system.[23] Positive remodelling was defined as a remodelling index >1.1. Plaques with a CT attenuation number <30 Hounsfield units were defined as low-attenuation plaques. Spotty calcification was defined as a calcium burden length <1.5 times the vessel diameter and a width less than two-thirds of the vessel diameter. High-risk plaques were defined by the presence of two or more high-risk plaque features, including positive remodelling, low-attenuation plaques, and spotty calcification. Obstructive plaque was defined as the presence of coronary luminal narrowing >50% in the left main coronary artery or >70% in any other coronary artery. Adverse CTA findings were defined as the presence of obstructive and/or high-risk plaques.

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 analysed using the paired Student's *t*-test and the Mann–Whitney *U*-test as appropriate. Categorical data were compared using χ^2 analysis or Fisher's exact test. Cumulative survival estimates were calculated using the Kaplan–Meier method and compared with the log-rank test. To ascertain the associations of HS with MACE, we performed univariate and multivariate Cox regression analyses, and the results were reported as hazard ratios (HRs) with 95% confidence interval (CI). To ascertain the independent predictors of MACE, we conducted a multivariate Cox regression analysis, which was performed by using the stepwise approach. The model included variables with $P < 0.10$ in the univariate analysis. The incremental value of HS compared with coronary CT findings in predicting MACE was assessed using the global χ^2 test, receiver operating characteristic curve analysis, and category-free net reclassification improvement. All reported *P* values were two-sided and $P < 0.05$ was considered statistically significant. Statistical analyses were performed using the SPSS software for Window, 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 and radiation dose

The patients' mean age was 64 ± 14 years, and 55% were male. Of these, 247 (22%), 231 (20%), and 216 (19%) patients had

CT-evidenced HS, obstructive plaque, and high-risk plaque, respectively. Baseline characteristics and coronary CTA results compared between patients with and without MACE are shown in *Table 1*. Patients with MACE were older and had greater body mass index and visceral adipose tissue area. They also showed higher prevalence of hypertension, diabetes mellitus, smoking habits, obesity, metabolic syndrome, and HS. Fibrosis-4 index did not differ between the two groups. Regarding the coronary CTA findings, patients with MACE had higher prevalence of adverse CTA findings than those without MACE. Baseline characteristics and coronary CTA results compared between patients with and without HS are shown in Supplementary material online, *Table S1*. The presence of obstructive and high-risk plaques in patients with HS was significantly higher than in those without HS. The mean dose-length product for abdominal CT was 226 mGy.cm, and the mean effective dose for each imaging modality was 3.39 mSv, using a conversion coefficient of 0.015.

Association of HS and CAD events in all patients

During a median follow-up of 3.9 years, 85 patients (24 and 61 of patients with and without HS, respectively) were censored at the time of revascularization because they were scheduled to undergo revascularization within 90 days based on indexed coronary CT findings, and MACE occurred in 23 patients with HS [cardiac death ($n = 2$), acute

Table 1 Patient demographics

	All patients ($n = 1148$)	MACE (+) ($n = 40$)	MACE (−) ($n = 1108$)	*P* value[a]
Age, years	64 ± 14	67 ± 11	63 ± 15	0.030
Male sex, *n* (%)	636 (55)	28 (70)	608 (55)	0.059
Body mass index, kg/m^2	24 ± 4	25 ± 5	24 ± 4	0.024
Visceral adipose tissue area, cm^2	94 ± 54	118 ± 50	93 ± 54	0.005
Hypertension, *n* (%)	676 (59)	31 (78)	645 (58)	0.015
Diabetes, *n* (%)	357 (31)	22 (55)	335 (30)	0.001
Dyslipidaemia, *n* (%)	552 (48)	23 (58)	529 (48)	0.225
Current smoker, *n* (%)	217 (19)	13 (33)	204 (18)	0.025
Obesity, *n* (%)	74 (6)	5 (13)	69 (6)	0.112
Metabolic syndrome, *n* (%)	274 (24)	19 (48)	255 (23)	<0.001
β-blockers, *n* (%)	237 (21)	12 (30)	225 (20)	0.137
CCBs, *n* (%)	394 (34)	19 (48)	375 (34)	0.074
ACE-Is or ARBs, *n* (%)	422 (37)	21 (53)	401 (36)	0.036
Statins, *n* (%)	354 (31)	13 (33)	341 (31)	0.817
Creatinine, mg/dL	0.90 ± 0.95	1.02 ± 1.30	0.89 ± 0.93	0.402
eGFR, mL/min/1.73 m^2	70 ± 19	68 ± 20	70 ± 19	0.663
AST, IU/L	24 ± 13	28 ± 16	24 ± 13	0.085
ALT, IU/L	24 ± 22	31 ± 23	24 ± 22	0.043
Total cholesterol, mg/dL	190 ± 36	192 ± 35	190 ± 36	0.678
LDL cholesterol, mg/dL	114 ± 32	122 ± 34	113 ± 32	0.123
HDL cholesterol, mg/dL	58 ± 17	53 ± 17	58 ± 17	0.088
Triglyceride, mg/dL	111 [82–163]	118 [85–170]	111 [81–162]	0.355
Haemoglobin A1c, %	6.3 ± 1.2	6.8 ± 1.2	6.3 ± 1.2	0.005
Fibrosis-4 index	1.7 ± 1.2	1.7 ± 1.0	1.7 ± 1.2	0.951
Framingham Risk Score, *n* (%)				<0.001
Low-risk	617 (54)	10 (25)	607 (55)	
Intermediate-risk	357 (31)	14 (35)	343 (31)	
High-risk	174 (15)	16 (40)	158 (14)	
Adverse CTA findings, *n* (%)	337 (29)	24 (60)	313 (28)	<0.001
High-risk plaque, *n* (%)	216 (19)	17 (43)	199 (18)	<0.001
Obstructive plaque, *n* (%)	231 (20)	16 (40)	215 (19)	0.001
Hepatic steatosis, *n* (%)	247 (22)	23 (58)	224 (20)	<0.001

Data are presented as mean ± standard deviation, *n* (%), or median [25th–75th percentile]. Adverse CTA findings are defined as the presence of obstructive and/or high-risk plaque.

ACE-Is, angiotensin–converting–enzyme inhibitors; ALT, alanine aminotransferase; ARBs, angiotensin receptor blockers; AST, aspartate aminotransferase; CCB, calcium channel blocker; CTA computed tomography angiography; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MACE, major adverse cardiac events.

[a]Comparison between MACE (+) and MACE (-).

coronary syndrome ($n = 10$), and late revascularization ($n = 11$)] and in 17 patients without HS [acute coronary syndrome ($n = 9$) and late revascularization ($n = 8$)]. As shown in *Table 2*, in the multivariate Cox regression analysis, HS was an independent predictor of MACE in a model that included CTA-verified high-risk and obstructive plaque (HR 4.01, 95% CI 2.12–7.59, $P < 0.001$). In addition, multivariate analysis of predictors for the composite of cardiac death and myocardial infarction was performed. HS remained an independent predictor of the composite of cardiac death and myocardial infarction (HR 7.86, 95% CI 2.68–23.03, $P < 0.001$) (Supplementary material online, *Table SII*). Kaplan–Meier curves show that the annual event rates for MACE significantly differed between patients with and without HS in patients with (4.75% vs. 1.50%; $P = 0.001$) and without (1.08% vs. 0.18%; $P < 0.001$) adverse CTA findings (*Figure 2A and B*). In the Cox proportional hazard analysis, HS was an independent predictor of MACE in patients with (HR 2.96, 95% CI 1.30–6.76, $P = 0.010$) and without (HR 6.34, 95% CI 2.29–17.53, $P < 0.001$) adverse CTA findings after adjustment for Framingham risk score. The addition of HS to FRS and adverse CTA findings significantly increased the global chi-square score from 29.0 to 49.5 ($P < 0.001$) (*Figure 3*). By adding HS to FRS and adverse CTA findings, the C-statistic significantly increased from 0.74 to 0.81 ($P = 0.026$). The net reclassification achieved by adding HS to FRS and adverse CTA findings was 0.746 ($P < 0.001$). Thus, the addition of HS to FRS and adverse CTA findings resulted in an improvement in the risk reclassification for MACE.

Association of HS and CAD events in patients with diabetes mellitus or metabolic syndrome

The additional predictive values of HS for MACE in patients with diabetes mellitus or metabolic syndrome were analysed. In 357 patients with diabetes mellitus, MACE occurred in 12 patients with HS [cardiac death ($n = 1$), acute coronary syndrome ($n = 6$), and late revascularization ($n = 5$)] and in 10 patients without HS [acute coronary syndrome ($n = 5$) and late revascularization ($n = 5$)]. Kaplan–Meier curves show that patients with HS had significantly higher incidence of MACE than those without HS (Supplementary material online, *Figure SIA*). HS was an independent predictor of MACE in patients with diabetes mellitus (HR 2.45, 95% CI 1.05–5.71, $P = 0.039$) (Supplementary material online, *Table SIII*). By adding HS to FRS and adverse CTA findings in patients with diabetes mellitus, global χ^2 scores also significantly increased from 6.9 to 13.3 ($P = 0.012$) and the net reclassification improvement yielded 0.530 ($P = 0.015$) (Supplementary material online, *Figure SIIA*). However, the increase in C-statistic was not significant (0.65–0.75, $P = 0.067$). In 274 patients with metabolic syndrome, MACE occurred in 15 patients with HS [cardiac death ($n = 1$), acute coronary syndrome ($n = 7$), and late revascularization ($n = 7$)] and in 4 patients without HS [acute coronary syndrome ($n = 2$) and late revascularization ($n = 2$)]. Kaplan–Meier curves showed that patients with HS had significantly higher incidence rates of MACE than those without HS (Supplementary material online, *Figure SIB*). HS was an independent predictor of MACE in patients with metabolic syndrome (HR 4.39, 95% CI 1.45–13.28, $P = 0.014$) (Supplementary material online, *Table SIV*). By adding HS to FRS and adverse CTA findings in patients with metabolic syndrome, global χ^2 scores also significantly increased from 10.4 to 21.6 ($P = 0.001$) (Supplementary material online, *Figure SIIB*). The net reclassification improvement yielded 0.779 ($P < 0.001$), while the increase in C-statistic was not significant (0.72–0.82, $P = 0.051$). Thus, the addition of HS to FRS and adverse CTA findings resulted in a moderate improvement in the risk reclassification for MACE in patients with diabetes mellitus and metabolic syndrome.

Discussion

We investigated the additional risk stratification benefits of HS concurrently assessed during coronary CTA in patients with suspected stable CAD in a large cohort. The main finding of this study is that HS

Table 2 Factors associated with major adverse cardiac events in all patients

	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	1.03 (1.00–1.06)	0.046		
Male, sex	2.34 (1.18–4.63)	0.014	2.08 (0.98–4.43)	0.030
Hypertension	2.58 (1.23–5.43)	0.012		
Diabetes mellitus	2.71 (1.45–5.05)	0.002		
Dyslipidaemia	1.51 (0.80–2.82)	0.202		
Body mass index	1.07 (1.00–1.15)	0.038		
Visceral adipose tissue area	1.01 (1.00–1.01)	0.003		
Current smoker	2.10 (1.18–3.72)	0.011		
ACE-Is or ARBs	2.05 (1.10–3.81)	0.024		
Framingham Risk Score	1.22 (1.12–1.33)	<0.001	1.19 (1.07–1.31)	<0.001
Fibrosis-4 index	1.04 (0.84–1.28)	0.737		
Hepatic steatosis	5.37 (2.87–10.05)	<0.001	4.01 (2.12–7.59)	<0.001
High-risk plaque	4.07 (2.17–7.62)	<0.001	1.89 (0.95–3.73)	0.069
Obstructive plaque	4.57 (2.41–8.65)	<0.001	2.43 (1.21–4.87)	0.012

ACE-Is, angiotensin–converting–enzyme inhibitors; ARBs, angiotensin receptor blockers; CI, confidential interval; HR, hazard ratio.

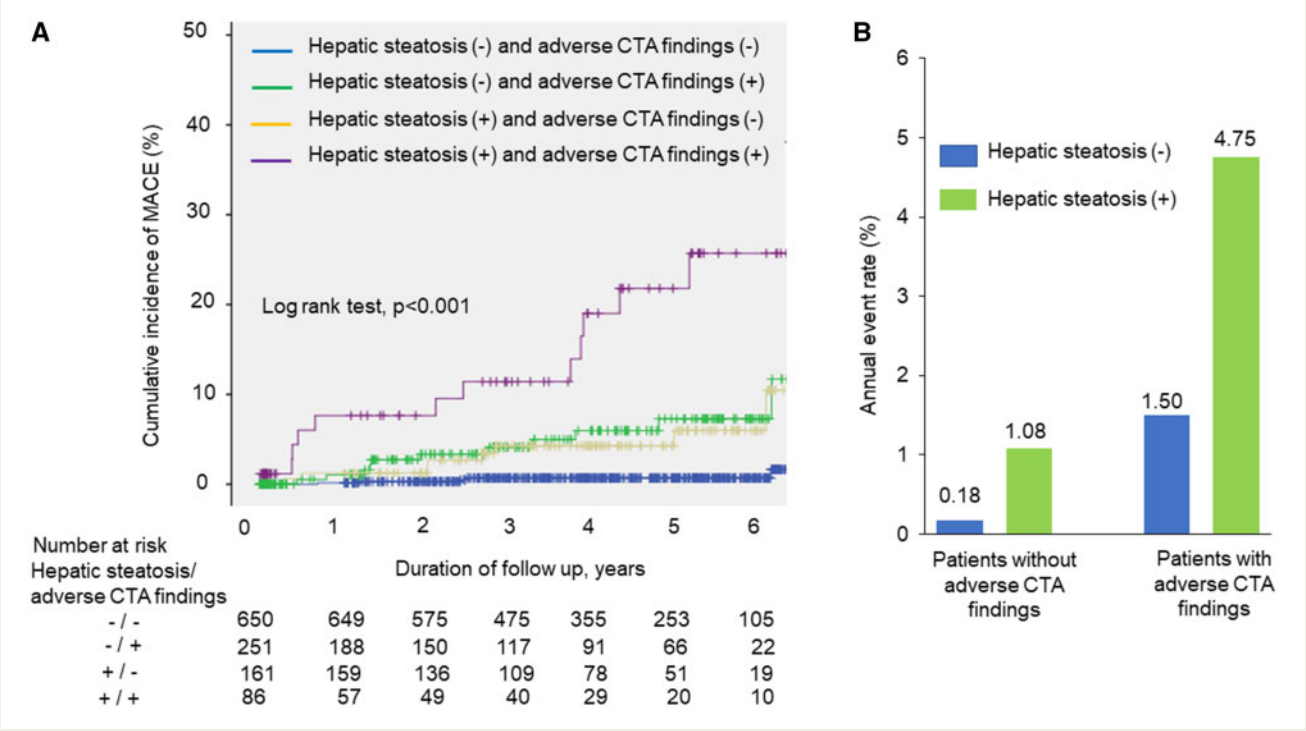


Figure 2 Impact of HS on MACE according to CTA findings. (*A*) Kaplan–Meier curves by the presence or absence of HS or adverse CTA findings for MACE. (*B*) Annual event rates for MACE by the presence or absence of HS or adverse CTA findings, which are defined as the presence of obstructive and/or high-risk plaque. CTA, computed tomography angiography; HS, hepatic steatosis; MACE, major adverse cardiac events.

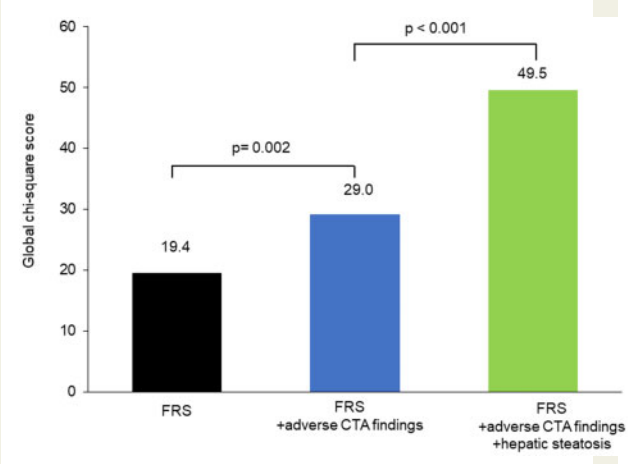


Figure 3 Incremental predictive value of HS over coronary CTA. Global χ^2 test to evaluate the model fitness by adding HS for the prediction of MACE over adverse CTA findings and Framingham risk score in all patients.

concurrently evaluated during coronary CTA, added to the adverse CTA findings (obstructive and/or high-risk plaque), improved the model fit, as well as the discriminative ability for predicting MACE in such patients. In addition, this study demonstrated that the prognostic value of HS remained significant in patients with diabetes mellitus and metabolic syndrome.

Several studies have reported that HS is an independent predictor of cardiovascular events.[9–11] We have reported the prognostic significance of HS assessed during coronary CTA; although our previous study included a small cohort ($n = 493$) of patients with suspected CAD.[13] In addition, in large studies of patients with suspected CAD, adverse coronary CTA findings have been associated with subsequent cardiovascular events,[2–5] while overall adverse coronary CTA findings have been found to have low positive predictive value for the identification of subsequent cardiovascular events. This study clearly demonstrated that patients with both HS and adverse coronary CTA findings had the worst outcomes at 4 years. These results suggest that the simultaneous identification of HS during coronary CTA will enable the detection of patients at higher risk of subsequent events and who therefore need more intensive preventive therapy.

Patients with HS often have metabolic comorbidities such as metabolic syndrome, diabetes mellitus, and dyslipidaemia.[24] Therefore, it is reasonable that there is a strong association between HS and an increased risk of MACE. However, the causal relationship between HS and MACE remains controversial. The circulating levels of interleukin-6, high-sensitivity C-reactive protein, and tumour necrosis factor-α reportedly increase in tandem with the histological severity of HS.[25,26] These cytokines are also well-established biomarkers of atherosclerotic plaque development, suggesting a pathophysiological link between HS and cardiovascular disease. A Mendelian

randomization study of the Danish general population reported that a genetic variant in the gene encoding patatin-like phospholipase domain-containing protein 3, which is a strong and specific cause of HS, was not causally associated with the risk of ischaemic heart disease.[27] Further studies are required to clarify the causal relationship between HS and cardiovascular events.

In clinical practice, ultrasonography and magnetic resonance imaging are used to diagnose fatty infiltration; however, CT may be a useful method of diagnosing liver fat.[12] Although the association between HS and cardiovascular disease has been established, the benefit of routine screening for HS in high-risk patients remains unclear. Based on our findings, in the setting of the evaluation of CAD with coronary CTA, the concurrent assessment of hepatic fatty content may benefit patients. The quantitative evaluation of HS by CT is advantageous because it enables greater consistency and is widely generalizable. However, we acknowledge several issues. The first concern is related to radiation. The average radiation in this study was 3.39 mSv, which is less than that of the usual abdominal scan, but apparently not negligible. The reduction of additional radiation exposure should be considered when selecting an optimal image acquisition method for liver fat. The second concern is related to cost; this study ignored cost constrains. Our findings would support the usefulness of concurrent evaluation of HS during coronary CTA in the risk assessment of future cardiovascular events. However, further investigations will be needed to elucidate this matter, with due consideration given to ethics and cost-effectiveness.

The 2019 European Society of Cardiology guidelines for the diagnosis and management of chronic coronary syndromes emphasize the importance of assessing pre-test probabilities and clinical likelihood of CAD.[28] Several studies have shown that HS is independently associated with subclinical atherosclerosis assessed by carotid intima-media thickness and coronary artery calcification.[29,30] In addition to subclinical atherosclerosis, patients with HS have a higher prevalence of clinically significant CAD requiring coronary revascularization.[31] Although our study indicated that HS screening by CT may provide useful information on the initial diagnostic management of patients with suspected CAD, HS screening by abdominal ultrasonography is an easy-to-use measure. Using this approach, we can facilitate risk stratification in patients with suspected CAD.

Study limitations

This study had some limitations. First, it was conducted in a single centre; therefore, its results require confirmation in a multicentre setting. Second, the study population was comprised solely by Japanese patients with suspected CAD. Although the event rate amongst our participants was low, it was similar with that shown in recent prospective CT trials that included 2802 Japanese patients.[32] However, our results cannot be applied to other ethnic groups or to the general population. Third, although this study focused on MACE associated with CAD, information on the acute coronary syndrome culprit lesions was not available because we obtained follow-up clinical information by either reviewing medical records or via telephone interviews. Fourth, HS was diagnosed via CT without histological confirmation of the liver status, which is the gold standard for diagnosis. Examination of the histological severity of HS requires liver biopsy, which should be considered in patients with suspected advanced fibrosis. Fifth, this study did not obtain information about inflammatory markers, change in medication, diet, physical activity, and risk factor control during the follow-up period, which may have affected the risk estimates of HS.

Conclusions

HS, concurrently evaluated during coronary CTA, improved the model fit and showed a discriminative ability for predicting MACE compared to adverse CTA findings (obstructive and/or high-risk plaque) in patients with suspected stable CAD. Our study outlines the feasibility of the simultaneous examination of HS during coronary CTA in assessing the risk of cardiovascular events. However, further investigation should be carried out before employing this method in clinical practice.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

Acknowledgements

The authors would like to thank Editage (https://www.editage.com/) for editing a draft of this manuscript.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Conflict of interest: none declared.

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