Impact of Non-Alcoholic Fatty Liver Disease on Cardiovascular Outcomes in Patients With Stable Coronary Artery Disease: A Matched Case–Control Study

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INTRODUCTION: Whether non-alcoholic fatty liver disease (NAFLD) is associated with cardiovascular risk has still been controversial. The reasons for this disparity may be associated with subject selection, events definition, diagnostic criteria of NAFLD, or research methods. The aim of this study was to determine the relationship of NAFLD to cardiovascular disease (CVD) outcomes in patients with stable, new-onset coronary artery disease (CAD).

METHODS: A matched case–control study based on the cohort with stable, new-onset CAD was implemented in 162 cases (patients who developed all-cause death, non-fatal myocardial infarction and stroke during an average of 11,484 patient-years of follow-up) and 162 controls without cardiovascular events matched with the same sex, the age difference ≤3 years old, and the admission date within 3 months. Abdominal ultrasonography and coronary angiography were performed at admission. COX proportional hazard models and conditional logistic regression analysis were used to assess the effect of NAFLD on CVD outcomes.

RESULTS: NAFLD was more common in the event group than in the control group ($P = 0.012$). Kaplan-Meier analysis showed a significant association between NAFLD and CVD outcomes ($P = 0.007$). Moreover, Cox regression (hazard ratios 1.56; 95% confidence interval, 1.04–2.34, $P = 0.031$) and conditional logistic regression (odds ratio 2.72, 95% confidence interval, 1.16–6.39, $P = 0.022$) analyses further demonstrated that NAFLD was an independent risk factor for CVD outcomes.

CONCLUSIONS: NAFLD is indeed an independent predictor of CVD outcomes in patients with stable, new-onset CAD. Further randomized controlled trials may be needed to confirm our findings.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) and cardiovascular disease (CVD) are 2 diseases that are common in the general population. Additionally, NAFLD is the most common cause of chronic liver disease. It has been recognized as the hepatic manifestation of obesity and the metabolic syndrome (MS) (1) and also a marker of pathological ectopic fat accumulation combined with a low-grade chronic inflammatory state. This results in several deleterious pathophysiological processes, including fatty acid and lipoprotein metabolism, abnormal glucose, increased oxidative stress, hypercoagulability, endothelial dysfunction, and accelerated progression of atherosclerosis (2–5).

Moreover, recent data suggest that NAFLD is linked to increased CVD risk, and accumulating evidence demonstrates that the clinical burden of NAFLD is not limited to liver-related morbidity and mortality, with the majority of deaths attributed to CVDs (3,6). Furthermore, it has been reported that NAFLD *per se* is a true risk factor for CVD, independently of classical known risk factors (3). As a result, the role of NAFLD as a potential independent CVD risk factor has gained considerable prominence and stimulated growing interest.

However, when it comes to the relationship of NAFLD to cardiovascular outcomes, the conclusions from existing studies were discordant (5,7–11). Thus, there is a hot debate on the

association between NAFLD with cardiovascular outcomes nowadays. The discrepancy of previous study results may be ascribed to the different subject selection, diagnosis criteria, study strategies, and events definition. What's more, few studies were found to explore the impact of NAFLD on clinical outcomes in patients with established coronary artery disease (CAD) (5,9). In addition, to our best knowledge, there have been no studies investigating the predicting role of NAFLD for cardiovascular events in angiography-proven, stable and new-onset CAD patients or taking all-cause deaths, non-fatal myocardial infarction (MI) and stroke as the composite endpoint events in their analysis. Thus, we undertook this matched case–control study to examine the relationship of NAFLD to cardiovascular outcomes using a large Chinese cohort.

METHODS

Study design and population

From March 2011 to July 2016, 7,164 consecutive Chinese patients who received coronary angiography because of angina-like chest pain and/or positive treadmill exercise test and/or significant stenosis indicated by coronary computed tomography angiography were considered for this analysis. On admission, 43 patients declined to participate. Based on elevated myocardial enzyme levels (cardiac troponin I, creatine kinase, and creatine kinase isoenzyme), typical electrocardiogram changes, and positive findings by coronary angiography, 787 non-CAD patients and 1937 CAD patients who had acute coronary syndrome (ACS) or a history of MI, percutaneous coronary intervention or coronary artery bypass grafting were excluded. Seven hundred twenty-one patients were rejected according to the exclusion criteria as follows: patients without abdominal ultrasound examination or with positive hepatitis B surface antigen; antibody against hepatitis C virus; autoimmune hepatitis; hereditary liver disease (e.g., hereditary hemochromatosis or Wilson's disease); excessive alcohol consumption (ongoing or recent alcohol consumption >21 standard drinks on average per week in men and >14 standard drinks on average per week in women) (12); secondary causes of fatty liver (e.g., chronic use of systemic corticosteroids or methotrexate) or drug-induced liver disease. Furthermore, 24 patients were lost to follow-up during the study. Thus, the resulting population consisted of 3,623 subjects with stable, new-onset CAD. After enrollment, optimal medical treatment (aspirin, clopidogrel, statins, β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, or calcium channel blockers), percutaneous coronary intervention, and coronary artery bypass grafting were provided as clinically indicated. Over an average of 11,484 patient-years of follow-up (median 3.2 years; interquartile range 2.1–4.1 years), a total of 162 patients developed hard cardiovascular events. Then, from the remaining pool of patients (n = 3,461), we randomly selected control subjects at a 1:1 ratio matched with the same sex, the age difference ≤3 years old, and the admission date within 3 months (Figure 1). Thus, there were 162 cases and 162 controls entering the final analysis.

The study complied with the Declaration of Helsinki and was approved by the hospital's ethical review board (Fu Wai Hospital and National Center for Cardiovascular Diseases, Beijing, China). Each participant provided written, informed consent before enrollment.
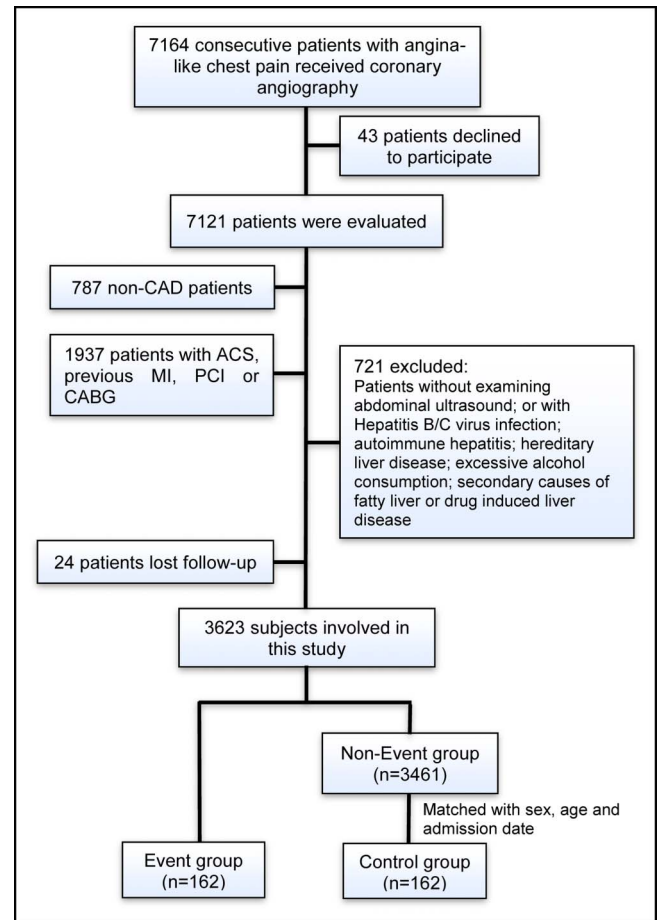

Figure 1. Flowchart illustrating study population. ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CAD, coronary artery disease; PCI, percutaneous coronary intervention.

Measurements and biochemical analysis

At baseline, during a personal interview, information on demographic factors, medical history, medication use, and personal health habits was collected from each subject. Anthropometric measurements were performed and blood pressure (BP) was measured. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Hypertension was defined as repeated BP measurements ≥140/90 mm Hg or self-reported hypertension and currently taking anti-hypertensive drugs. Diabetes mellitus (DM) was defined as a fasting plasma glucose level ≥7.0 mmol/L in multiple determinations or random plasma glucose ≥11.0 mmol/L or the 2-hour plasma glucose of the oral glucose tolerance test ≥11.0 mmol/L or using hypoglycemic medications currently. MS was diagnosed according to the Chinese Diabetes Society's advice in 2004 (13). Based on these criteria, patients were defined with MS when they had any three or all of the following items: (i) BMI ≥ 25.0 kg/m²; (ii) fasting plasma glucose level ≥6.1 mmol/L or 2-hour plasma glucose of the oral glucose tolerance test ≥7.8 mmol/L or being diagnosed with DM and under hypoglycemic medications treatment currently; (iii) BP ≥ 140/90 mm Hg or being diagnosed with hypertension and currently taking anti-hypertensive drugs; (iv) fasting plasma triglyceride ≥1.7 mmol/L or high-density lipoprotein cholesterol <0.9 mmol/L in men or <1.0 mmol/L in women. The baseline

Table 1. Basic information distribution in the event and control groups

	Events n = 162	Controls n = 162	P value
Age, yr	61.2 ± 9.1	61.1 ± 8.8	0.847
Male, %	64.8	64.8	1.000
Hypertension, %	75.3	64.2	0.029
DM, %	32.1	33.3	0.813
MS, %	50.0	36.4	0.014
NAFLD, %	25.3	14.2	0.012
Current smokers, %	33.8	40.1	0.236
Family history of CAD, %	12.1	15.2	0.425
BMI, kg/m^2	25.97 ± 3.20	25.26 ± 2.99	0.042
SBP, mm Hg	129.5 ± 19.5	126.0 ± 15.1	0.075
DBP, mm Hg	77.0 ± 12.2	76.4 ± 9.4	0.670
LVEF, %	62.3 ± 8.1	64.2 ± 6.4	0.027
Gensini score	34.5 (17.0–64.5)	22.0 (10.0–42.5)	<0.001
Revascularization, %	60.4	48.7	0.040
Biochemistry parameters			
TC, mmol/L	4.22 ± 1.29	4.10 ± 1.14	0.392
HDL-C, mmol/L	1.06 ± 0.29	1.09 ± 0.30	0.377
LDL-C, mmol/L	2.42 ± 0.90	2.43 ± 0.88	0.903
Triglyceride, mmol/L	1.63 (1.14–2.30)	1.40 (0.99–1.87)	0.012
Lipoprotein a, mg/L	187.88 (67.98–422.86)	134.74 (57.15–332.90)	0.142
FPG, mmol/L	6.04 ± 1.97	5.59 ± 1.28	0.016
HbA1c, %	6.60 ± 1.33	6.36 ± 0.90	0.059
Creatinine, umol/L	78.57 ± 17.68	72.58 ± 13.79	0.001
HsCRP, mg/L	1.78 (0.88–4.02)	1.20 (0.62–2.75)	0.001
ALT, U/L	24 (16–38)	21 (15–28)	0.041
AST, U/L	19 (15–25)	17 (13–23)	0.057
GGT, U/L	29 (21–45)	24 (18–35)	0.008
ALP, U/L	64 (55–81)	63 (54–75)	0.068
Medications at admission			
Aspirin, %	84.0	85.3	0.811
Statins, %	9.4	17.5	0.033
ACEI/ARB, %	23.1	27.0	0.574
β-blockers, %	47.5	47.3	0.980
CCB, %	22.8	27.0	0.544

The listed variables in the table were available for all patients. Continuous values are summarized as mean ± s.d., median (interquartile range) and categorical variables as percentage.
ACEI, angiotensin-converting enzyme inhibitors; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ARB, angiotensin receptor blockers; AST, aspartate aminotransferase; BMI, body mass index; CAD, coronary artery disease; CCB, calcium channel blockers; DBP, diastolic blood pressure; DM, diabetes mellitus; FPG, fasting plasma glucose; GGT, gamma-glutamyl transpeptidase; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; SBP, systolic blood pressure; TC, total cholesterol.

angiographic data were collected from catheter laboratory records by 3 interventional cardiologists, and the coronary severity was evaluated by calculating Gensini score (14). This score was computed by assigning a severity score to each coronary lesion according to the degree of luminal narrowing and the importance of location, and the total score equaled the sum of the severity score times the location score for all diseased segments (14).

Blood samples were collected into ethylenediaminetetraacetic acid-containing tubes from each patient after at least 12-hour fasting in the morning. Liver enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), alkaline phosphatase (ALP) as well as lipid profiles total cholesterol, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, etc., were measured using an automatic biochemistry analyzer (Hitachi 7150, Tokyo, Japan) and enzymatic assay. The other related biomarkers were analyzed by standard commercial kits.

Assessment of fatty liver by ultrasonography

Abdominal ultrasonography was performed by 2 experienced sonographers who were unaware of the participants' clinical and laboratory characteristics at the time of the procedure using the Philips Ultrasound Machine (EPIQ7; Philips, Bothell, WA). The diagnosis of the fatty liver required ultrasonographic features of diffusely increased liver echogenicity greater than that of the kidney or spleen, vascular blurring, and deep attenuation of the ultrasound signal (15).

Follow-up

After the initial appointment, all patients were actively followed up at 6-month intervals after hospital discharge by well-trained nurses or cardiologists who were blinded to the aim of this study. Follow-up information was obtained from telephone communications and/or face-to-face interviews. The cardiovascular events were defined as all-cause death (death mainly caused by CVDs), non-fatal MI, and stroke. The follow-up time interval (months) was counted from the enrollment till the last traceable hospital inpatient or outpatient record or telephone interview before February 28, 2018. All available relevant data from any reported possible event were collected. Death of a participant was reported by the relatives, general practitioner, or specialist who treated the participant. Three experienced cardiologists who were masked to any of the study data classified the events independently.

Statistical analysis

Continuous variables are expressed as mean ± s.d. or median with interquartile range as appropriate, and differences between groups were determined using the Student's t test, analysis of variance, or nonparametric test. Categorical variables were presented as number (percentage) and analyzed by χ^2 statistic test or Fisher's exact test. The cumulative event-free survival rates of patients with and without NAFLD were estimated by the Kaplan-Meier method and compared by the log-rank test. However, Kaplan-Meier curve is not a reliable test outside of randomized, evenly matched groups due to the potential influence of confounding variables and therefore cannot be reliably interpreted for survival in unevenly matched groups. Therefore, Cox proportional hazard models were further performed to calculate hazard ratios (HRs) for cardiovascular events of the presence of NAFLD and also each 10 U/L increase in liver enzymes. The analyses were initially performed adjusting for age and sex in model 1; further adjustments were subsequently made for hypertension, DM, Gensini score, left ventricular ejection fraction, creatinine, and high-sensitivity C-reactive protein in model 2, and all these risk factors plus statin use in model 3. In addition, we adjusted for age, sex, MS, Gensini score, left ventricular ejection fraction, creatinine, and high-sensitivity C-reactive protein in Cox hazard model 4. Conditional logistic regression analysis was

used to further assess the impact of NAFLD and liver enzymes on 3-year cardiovascular events risk in patients who completed 3-year follow-up, adjusting for the same confounding factors with model 3 and model 4. The statistical analysis was performed with SPSS version 22.0 software (SPSS, Chicago, IL). For all analyses, 2-tailed P values < 0.05 were considered statistically significant.

RESULTS

Baseline characteristics

The demographics and clinical characteristics of the event and control groups are described in Table 1. The average age of the whole population was 61.2 years old and 64.8% (n = 210) of them were male. Clearly, patients in the event group had higher percentages of hypertension, MS, NAFLD, and revascularizations (all $P < 0.05$). Meanwhile, the event group had higher levels of BMI, Gensini score, triglyceride, fasting plasma glucose, creatinine and high-sensitivity C-reactive protein, and lower levels of left ventricular ejection fraction ($P < 0.05$, respectively). In addition, liver enzyme ALT ($P = 0.041$) and GGT ($P = 0.008$) levels were significantly higher in the event group compared with the control group, while the difference in AST and ALP levels between these two groups had no statistical significance (both $P > 0.05$). Furthermore, with respect to the prescribed medications at baseline, the event group had a much lower percentage of statin use compared with the control group ($P = 0.033$), while the use of the other drugs was similar between the two groups (all $P > 0.05$). Because of the initial diagnosis of CAD in our subjects, there was an extremely low percentage of them treated with statins and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

NAFLD, liver enzymes, and cardiovascular outcomes

Over an average of 11,484 patient-years of follow-up, 162 hard endpoint events were recorded, including 44 (27.16%) deaths, 39 (24.07%) non-fatal MIs, and 79 (48.77%) strokes. Among all mortality events, 30 (68.18%) patients died of CVD, 11 (25.00%) patients died of cancer, and 3 (6.82%) patients died of accident. Meanwhile, there were 10 deaths, 11 non-fatal MIs, and 20 strokes among patients with NAFLD, while 34 deaths, 28 non-fatal MIs, and 59 strokes among patients without NAFLD. The Kaplan-Meier analysis demonstrated that there was a significant difference in the event-free survival rates between patients with and without NAFLD ($P = 0.007$, Figure 2.). As shown in Table 2,
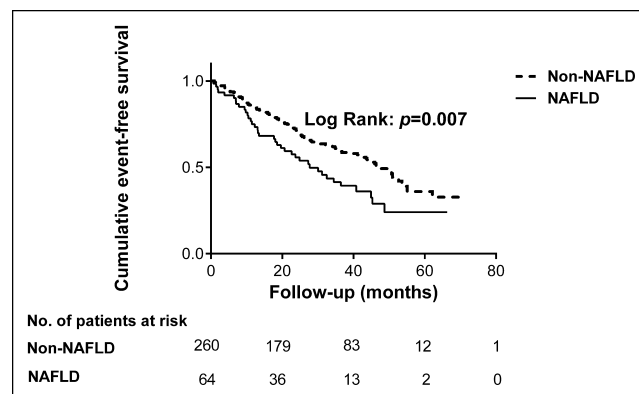

Figure 2. The cumulative event-free survival analysis according to the presence or absence of NAFLD. NAFLD, non-alcoholic fatty liver disease.

Table 2. Univariate Cox proportional hazards regression analysis of the composite endpoint events

Variables	HR	95% CI	P value
Age	1.01	0.99–1.02	0.605
Male	0.99	0.71–1.39	0.963
BMI	1.05	0.99–1.10	0.080
Hypertension	1.28	0.89–1.85	0.182
DM	1.06	0.84–1.34	0.608
MS	1.49	1.08–2.05	0.015
NAFLD	1.66	1.15–2.42	0.007
Current smoking	0.77	0.55–1.08	0.130
LVEF	0.98	0.96–1.00	0.038
Gensini score	1.01	1.00–1.01	0.001
Revascularization	1.19	0.86–1.66	0.295
Triglyceride	1.03	0.97–1.10	0.370
Creatinine	1.02	1.01–1.03	<0.001
HsCRP	1.06	1.01–1.10	0.013
ALT[a]	1.08	1.02–1.15	0.013
AST[a]	1.13	0.97–1.31	0.112
GGT[a]	1.01	0.98–1.03	0.606
ALP[a]	1.06	0.99–1.13	0.075
Statin use	0.55	0.32–0.96	0.035

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; GGT, gamma-glutamyl transpeptidase; HR, hazard ratio; HsCRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction; MS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease.
[a]Each 10 U/L increase.

a baseline NAFLD had a 1.66 × higher risk of the occurrence of cardiovascular events compared with the non-NAFLD group in the univariate Cox proportional hazards regression analysis. Additional adjustments for multiple variables in 3 models did not change this association (all $P < 0.05$; Tables 3–5), and NAFLD was still significantly and independently associated with the risk of cardiovascular events (HRs, 1.56; 95% confidence interval (CI), 1.04–2.34; Table 5). Moreover, after adjusting for MS and other potential confounding factors, the predicting role of NAFLD in cardiovascular outcomes remained unchanged (HR, 1.62; 95% CI, 1.09–2.39; Table 6). Among liver enzymes ALT, AST, GGT, and ALP, only ALT had a significant and independent association

Table 3. Multivariate Cox proportional hazard model 1 in predicting composite endpoint events

Variables	HR	95% CI	P value
Age	1.009	0.990–1.028	0.605
Male	0.988	0.704–1.386	0.942
NAFLD	1.725	1.180–2.522	0.005

CI, confidence interval; HR, hazard ratio; NAFLD, non-alcoholic fatty liver disease.

with cardiovascular outcomes, with an adjusted HR of 1.09 (95% CI, 1.02–1.17) for each 10 U/L increase in it. The following conditional logistic regression analysis further demonstrated the association of NAFLD and each 10 U/L increase in ALT with 3-year risk of cardiovascular events (137 events and 137 controls) after adjusting for the same confounding factors with model 3 (NAFLD: odds ratio (OR), 2.72; 95% CI, 1.16–6.39; ALT: OR, 1.19; 95% CI, 1.01–1.40) and model 4 (NAFLD: OR, 2.23; 95% CI, 1.15–4.34; ALT: OR, 1.13; 95% CI, 1.00–1.27). Moreover, a sub-analysis exploring the association of NAFLD (HR, 1.56; 95% CI, 1.02–2.38) and ALT (HR, 1.08; 95% CI, 1.01–1.15; for each 10 U/L increase of ALT) with composite endpoint events inclusive of specific cardiovascular death, non-fatal MI, and stroke showed similar results with the above analysis of primary endpoint events after adjusting for the confounding factors.

DISCUSSION

In this matched case–control study on new-onset CAD patients undergoing coronary angiography, we found that NAFLD was associated with cardiovascular outcomes independently of other demographic and metabolic factors and that NAFLD-induced increase in ALT also had a significant association with cardiovascular prognosis. These results may provide additional and novel information for the association of NAFLD with clinical prognosis in patients with stable, new-onset CAD.

NAFLD is a common liver disease, affecting as high as a third of the population worldwide, and may confer increased cardiometabolic risk with consequent adverse cardiovascular outcomes independent of traditional CVD risk factors and the MS. It is usually characterized by insulin resistance and is strongly associated with obesity and type 2 DM (3) and has been regarded as the liver manifestation of MS, a highly atherogenic condition (1). Since NAFLD and MS are closely related, previous studies have suggested that patients with NAFLD have an increased CVD risk. There is a growing body of epidemiological and experimental evidence suggesting that NAFLD predisposes to atherogenic dyslipidemia, deteriorates hepatic or peripheral insulin resistance, and releases a variety of proinflammatory, procoagulant, thrombogenic factors that may promote the development of CVD, type 2 DM, and so on (11). In fact, Choi et al. (16) indicated that NAFLD is associated with an elevated 10-year risk of developing CAD as estimated using Framingham risk score and independently related to the risk of developing CAD, regardless of classical risk factors and other components of MS. Moreover, NAFLD is also demonstrated to be associated with coronary artery calcification, endothelial dysfunction, and coronary stenosis (2,9,17,18).

However, studies on the association between NAFLD and cardiovascular outcomes have not reached a consensus conclusion yet. The discordance of these study results may be explained by the differences in their subject selection, events definition, diagnostic criteria of NAFLD, or research methods. In the general population, Fracanzani et al. (4) indicated that NAFLD was independently related to the cardiovascular events including ACS, revascularization, and stroke. Hamaguchi et al. (19) reported that NAFLD was a strong predictor of CVD outcomes and might play a central role in the cardiovascular risk of MS. Treeprasertsuk et al. (20) demonstrated that NAFLD was associated with a 10-year CVD risk defined by congestive heart failure, ACS, a flow-limiting stenosis from angiography, or angina requiring revascularization. Meanwhile, in a multiethnic study, researchers

LIVER

Table 4. Multivariate Cox proportional hazard model 2 in predicting composite endpoint events

Variables	HR	95% CI	P value
Age	1.00	0.98–1.02	0.925
Male	0.71	0.49–1.04	0.076
Hypertension	1.18	0.80–1.74	0.411
DM	0.97	0.76–1.23	0.785
Gensini score	1.00	1.00–1.01	0.082
LVEF	0.99	0.97–1.01	0.335
Creatinine	1.02	1.01–1.03	<0.001
HsCRP	1.04	0.99–1.09	0.090
NAFLD	1.67	1.12–2.48	0.012

CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; HsCRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction; NAFLD, non-alcoholic fatty liver disease.

Table 6. Multivariate Cox proportional hazard model 4 in predicting composite endpoint events

Variables	HR	95% CI	P value
Age	1.00	0.98–1.02	0.809
Male	0.71	0.49–1.04	0.077
MS	1.31	0.93–1.83	0.118
Gensini score	1.00	1.00–1.01	0.076
LVEF	0.99	0.97–1.02	0.487
Creatinine	1.02	1.01–1.03	<0.001
HsCRP	1.04	0.99–1.09	0.076
NAFLD	1.62	1.09–2.39	0.017

CI, confidence interval; HR, hazard ratio; HsCRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction; MS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease.

found that NAFLD could predict all-cause mortality and incident cardiovascular events (MI, resuscitated cardiac arrest, angina, or coronary revascularizations) (21). Nonetheless, there was only a trend towards association between hepatic steatosis and cardiovascular prognosis in Mellinger et al.'s study (10) with the events defined by non-fatal MI, stroke, transient ischemic attack, heart failure, or peripheral arterial disease and no significant relationship between them in Pickhardt et al.'s study (22) with the events diagnosed as MI, cerebrovascular accident, transient ischemic attacks, and coronary bypass grafting or stenting. In type 1 diabetic patients, Mantovani et al.'s (23) study showed that NAFLD is associated with an increased risk of incident cardiovascular events (nonfatal ischemic heart disease, nonfatal ischemic stroke, or coronary or peripheral artery revascularizations). NAFLD can also predict the risk of cardiovascular events including nonfatal MI, revascularizations, ischemic stroke, and cardiovascular deaths in type 2 diabetic adults (24). At the same

Table 5. Multivariate Cox proportional hazard model 3 in predicting composite endpoint events

Variables	HR	95% CI	P value
Age	1.00	0.98–1.02	0.871
Male	0.76	0.52–1.11	0.149
Hypertension	1.19	0.81–1.76	0.382
DM	0.96	0.75–1.23	0.743
Gensini score	1.00	1.00–1.01	0.065
LVEF	0.99	0.96–1.01	0.187
Creatinine	1.02	1.01–1.03	<0.001
HsCRP	1.03	0.98–1.08	0.221
Statin use	0.60	0.33–1.06	0.080
NAFLD	1.56	1.04–2.34	0.031

CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; HsCRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction; NAFLD, non-alcoholic fatty liver disease.

time, Perera et al. (25) suggested that patients with NAFLD had a higher predicted mortality from acute MI (AMI), and Keskin et al. (26) demonstrated that NAFLD revealed a higher incidence of major adverse cardiac events consisting of all-cause death, non-fatal AMI, and/or target lesion revascularization in patients with ST-segment elevation MI. Moreover, in patients with chronic heart failure, NAFLD fibrosis score was independently associated with cardiovascular events including cardiovascular deaths, MI, stroke, sudden cardiac death, and rehospitalization due to worsening heart failure (27). However, Karajamaki et al. (28) found that NAFLD with MS implied a considerable risk of cardiovascular events (coronary artery revascularizations, cardiovascular death, and stroke), whereas NAFLD without MS did not. Moreover, in patients with angiography-proven CAD, Wong et al. (5,9) reported that NAFLD could not predict cardiovascular mortality, ACS/non-fatal MI, secondary coronary interventions, and hospitalization for congestive failure. Excepting a handful of researches diagnosing NAFLD with histology, most of the previous studies defined NAFLD through abdominal ultrasound. Meanwhile, there were also some studies using abdominal computed tomography (10,20–22) or liver enzymes (29–31) to diagnose NAFLD. Different diagnostic methods of NAFLD may also influence the study results. Moreover, throughout the studies on the association between NAFLD and cardiovascular outcomes, most of them were prospective, but there were still some retrospective ones (7,23), especially the studies conducted 10 years ago. The difference in research methods may contribute to the disparity of existing studies as well. Based on these situations and similar to most studies, we observed a significant association between NAFLD and cardiovascular events defined by all-cause death/cardiovascular death, non-fatal MI, and stroke independently of other metabolic factors including MS. It is noteworthy that differing from Karajamaki et al. ' study (28), we did not find that MS could interfere with the association between NAFLD and cardiovascular outcomes. Nevertheless, MS was defined using the criteria of Chinese Medical Association (13) but not revised National Cholesterol Education Program Adult Treatment panel III (NCEP-ATP III) (32) or International Diabetes Federation (33) in our study, since we did not have data on waist circumference, which may be a minor flaw. But above all, our study population was a cohort of patients with stable,

new-onset CAD, which has not been explored before. Thus, the findings of the present study may provide more evidence for the conception that NAFLD is an independent risk factor for cardiovascular outcomes.

In addition, aminotransferase, especially ALT, has been regarded as a representative marker of NAFLD after the exclusion of other liver diseases (34–36). Martin-Rodriguez et al. (35) indicated that serum ALT seems to be a pretty good biomarker of liver fat accumulation and is positively correlated with liver triglyceride quantification. However, many other studies suggested that ALT levels are relatively insensitive markers of NAFLD (11) and that it cannot be used to predict the severity of NAFLD (37, 38). Furthermore, when it comes to the association between ALT and cardiovascular outcomes, the conclusions of related studies have also been discordant (6,31,36,39,40). In the present study, we found that patients with cardiovascular events had higher baseline ALT levels and that ALT was significantly associated with cardiovascular outcomes.

Our study is limited by several facts. First, as inherent to the nature of any prospective and observational study, our findings are subject to confounding factors, and also the level of risk factors at the baseline examination might change during the follow-up. Second, the sample size and follow-up time of this study were relatively small and short. However, a case–control study just does not require that large sample size. Moreover, our study is still continuing in order to better examine the prognostic value of NAFLD in the long-term cardiovascular outcomes in the future. Third, given the restrictions of the cardiovascular specialist hospital, we could not perform liver biopsy, which is considered as the gold standard to diagnose NAFLD. However, we minimized bias by restricting the examination to 2 experienced operators. In addition, we could also evaluate the cardiovascular outcomes professionally and reliably as cardiologists.

In this matched case–control study with a Chinese cohort of stable, new-onset CAD, data suggested that NAFLD was an independent predicator of cardiovascular outcomes and that NAFLD-induced elevation of ALT was also positively associated with cardiovascular prognosis. This result is undoubtedly significant as it provides important clinical implications for screening and surveillance strategies of NAFLD in patients with stable CAD. Thus, for CAD patients with NAFLD, medical management and moderate lifestyle modification with regard to NAFLD may be appropriate and should be recommended to improve long-term clinical prognosis.

CONFLICTS OF INTEREST

Study Highlights

WHAT IS KNOWN

✔ NAFLD and CVD are common in the general population.
✔ Whether NAFLD is associated with cardiovascular risk has still been controversial.

WHAT IS NEW HERE

✔ This is a strictly matched case–control study.
✔ NAFLD was common in patients with cardiovascular events.
✔ NAFLD could predict clinical prognosis in patients with stable CAD.

TRANSLATIONAL IMPACT

✔ NAFLD may be used for risk stratification and a novel treatment target in CAD patients.

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