Non-alcoholic fatty liver disease and outcomes in persons with acute coronary syndromes: insights from the GRACE-ALT analysis

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ABSTRACT

Objective Non-alcoholic fatty liver disease (NAFLD) is associated with a higher risk of cardiovascular disease, but no data exist about the relation between NAFLD and adverse outcomes in persons with acute coronary syndromes (ACS). We evaluated elevated serum alanine aminotransferase (ALT) as a marker of NAFLD, in association adverse outcomes following ACS.

Methods We conducted a retrospective cohort study of participants enrolled in the Global Registry of Acute Coronary Events (GRACE) admitted for ACS to St Michael's Hospital, Toronto, between 1999 and 2007. Multivariable linear regression was used to determine the change in maximum measured cardiac troponin I (cTnI) per each 1 IU/l increase in serum ALT concentration. The association between an elevated ALT >90th centile, and adverse outcomes in-hospital and at 6 months were calculated using multiple logistic regression analyses, adjusting for age, sex, body mass index, serum creatinine, glucose, triglycerides and LDL-C, as well as chronic statin or other lipid-lowering agent use.

Results 528 participants were included. Each 1 IU/l increase in ALT was associated with an increase in maximum measured cTnI of 0.16 μg/l (95% CI 0.10 to 0.22). An elevated ALT concentration >90th percentile was associated with a maximum measured cTnI in the highest quartile (adjusted OR 7.07, 95% CI 1.83 to 27.37). An elevated ALT >90th percentile was also significantly associated with all-cause mortality in-hospital, and up to 6 months after discharge (adjusted OR 8.96, 95% CI 3.28 to 24.49).

Conclusions NAFLD, determined by an elevated serum ALT, is associated with a higher risk of adverse outcomes in persons with ACS. Whether ALT is a valid and independent prognostic marker in ACS remains to be determined.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) affects 20%–30% of adults in the US, and the prevalence is predicated to rise to 50% by the year 2030.[1 2] NAFLD comprises a spectrum ranging from simple steatosis (fatty infiltration of the liver) to inflammatory steatohepatitis (NASH), to possible long-term injury (fibrosis and cirrhosis).[3] Its underlying predisposing cardiometabolic traits are those of insulin resistance, abdominal obesity and dyslipidemia; NAFLD occurs in 70%–90% of those with recognised type 2 diabetes mellitus (DM2).[1 4 5]

Long-term epidemiological studies have assessed the risk of cardiovascular disease (CVD) in association with NAFLD, using serum alanine aminotransferase (ALT)—a sensitive and inexpensive biochemical marker of NAFLD.[6–8] No data exist about the association between NAFLD and outcomes in patients with acute coronary syndromes (ACS).

OBJECTIVE

We studied the association between serum ALT concentration after ACS hospitalisation, and both the degree of myocardial necrosis and adverse outcomes arising in-hospital and at 6 months.

METHODS

We conducted a prospective cohort study using participants from the Global Registry of Acute Coronary Events (GRACE), an international observational database tracking outcomes of patients hospitalised with a diagnosis of suspected ACS.[9]

Briefly, GRACE included adults aged 18 years and older suspected to have ACS in the absence of a significant comorbidity, such as a motor vehicle crash, trauma, severe gastrointestinal bleeding, surgery or a medical procedure. They were admitted to a participating hospital upon ACS-related symptoms, and could be transferred from a non-registry hospital as well. Patients had to be at least 18 years old, have symptoms consistent with cardiac ischaemia, and at least one of the following: abnormal cardiac biomarkers, ECG changes consistent with ACS, and/or a documented history of coronary artery disease. Patients who died within 1 day of hospital admission were also enrolled if the cause of death was ACS.[9] A six-page standardised data abstraction form across all participating hospitals was used to collect information on patient baseline measures, such as past medical history, medications, electrocardiographic findings, and hospital-associated outcomes upon enrolment into GRACE. Six-month follow-up contact of discharged patients from all hospitals was also carried out.[9]

The current analysis was limited to GRACE participants admitted to St Michael's Hospital in downtown Toronto between April 1999 and December 2007. Additional variables were collected from the clinical database at St Michael's Hospital, and included a first serum ALT concentration in the index admission, and the timing of the ALT measurement. As documented in the admission or discharge summary notes of the hospital clinical database, we excluded individuals with a documented history of autoimmune or viral hepatitis, excess alcohol consumption or substance use.

Table 1 Baseline characteristics of participants with and without a measured serum alanine aminotransferase (ALT) within 5 days of hospital admission for suspected acute coronary syndrome

	ALT measured?		
Characteristic*	**Yes (n=528)**	**No (n=587)**	**p Value**
Demographic			
Mean (SD) age, years	63.4 (12.4)	64.3 (12.2)	0.7
Male	402 (68.5)	384 (67.1)	0.6
Mean (SD) body mass index, kg/m^2	28.4 (5.4)	28.1 (5.3)	0.7
Past medical history before index hospitalisation			
Cardiovascular disease†	438 (74.6)	464 (81.1)	0.008
Type 2 diabetes mellitus	165 (28.2)	137 (24.2)	0.1
Hyperlipidaemia	336 (57.5)	334 (59.5)	0.6
Renal dysfunction	59 (10.2)	30 (5.3)	0.002
Current or ex-smoker	338 (58.0)	328 (58.1)	1.0
Chronic medical therapy before index hospitalisation			
Aspirin	217 (37.1)	261 (45.7)	0.003
Clopidogrel	39 (9.3)	30 (8.6)	0.8
Statin or other lipid-lowering agent	273 (62.2)	166 (31.4)	0.005
Signs and symptoms at index hospitalisation			
Acute coronary syndrome type			
ST-elevation myocardial infarction	288 (49.3)	235 (41.2)	0.0006
Non-ST elevation myocardial infarction	191 (31.7)	172 (30.1)	
Unstable angina	76 (13.0)	125 (21.9)	
Other	29 (5.0)	39 (6.8)	
Killip class			
I	475 (81.3)	471 (83.4)	0.7
II	76 (13.0)	69 (12.2)	
III	27 (4.6)	22 (3.9)	
IV	6 (1.0)	3 (0.53)	
Cardiac arrest at admission	20 (3.4)	15 (2.6)	0.4
Mean (SD) systolic blood pressure, mm Hg	137.3 (30.2)	137.3 (27.8)	1.0
Mean (SD) diastolic blood pressure, mm Hg	80.8 (18.4)	80.4 (17.0)	0.7
Mean (SD) pulse rate, beats per minute	77.4 (21.5)	77.7 (23.8)	0.8
Biochemical measures at index hospitalisation			
Mean (SD) fasting or non-fasting plasma glucose, mmol/l	7.7 (4.9)	6.9 (3.1)	0.2
Mean (SD) serum creatinine, μmol/l	111.3 (77.9)	103.6 (59.8)	0.07
Mean (SD) serum total cholesterol, mmol/l	4.5 (1.3)	4.5 (1.1)	0.5
Mean (SD) serum LDL-cholesterol, mmol/l	2.7 (0.51)	2.7 (0.92)	1.0
Mean (SD) serum triglycerides, mmol/l	1.8 (1.7)	1.71 (1.4)	0.4
Events arising after index hospitalisation			
Mean (SD) maximum cTnI level ≤24 h of index admission, μg/l	26.7 (35.1)	21.05 (30.3)	0.004
All-cause in-hospital mortality during the index hospitalisation	76 (13.0)	52 (9.1)	0.04
All-cause mortality at 6 months after index hospitalisation	86 (14.7)	63 (11.0)	0.07
Composite of myocardial infarction, stroke, rehospitalisation or all-cause mortality at 6 months after index hospitalisation	155 (38.3)	144 (46.8)	0.02

*Data are presented as n (%) percentage, unless otherwise specified.
†Includes angina, atrial fibrillation, coronary artery disease, cardiac arrest, heart failure, hypertension, myocardial infarction, peripheral arterial disease, transient ischemic attack or stroke

The study exposure was the first ALT concentration measured within 5 days of the index hospitalisation for ACS. An elevated ALT was defined as a sex-specific value ≥90th percentile among the cohort. The primary study outcome was the maximum measured cardiac troponin (cTnI) level within the first 24 h of hospital admission. cTnI is a valuable predictive tool for adverse outcomes in patients with ACS.[10–13] Secondary outcomes included all-cause mortality in-hospital, all-cause mortality in-hospital and up to 6 months after discharge, and a composite of myocardial infarction, stroke, rehospitalisation or all-cause mortality up to 6 months after discharge.

The study was approved by the research ethics board of St Michael's Hospital.

Data analysis

Linear regression was used to assess the maximum-measured cTnI within the first 24 h after admission (measured in μg/l) per each 1 IU/l unit increase in serum ALT concentration. The model adjustment variables included age (continuous in years), sex, body mass index (continuous in kg/m^2), first-measured serum creatinine (continuous in μmol/l), first fasting or non-fasting plasma glucose (continuous in mmol/l), first fasting serum triglycerides and serum LDL-C (continuous in mmol/l), and recorded chronic statin or other lipid-lowering agent use.

Maximum cTnI levels within the first 24 h were then divided into quartiles. Crude and adjusted OR were calculated for each cTnI quartile in association with a sex-specific

Table 2 Association between serum alanine aminotransferase (ALT) and severity of maximum-measured cardiac troponin (cTnI) elevation within 24 h of hospital admission for suspected acute coronary syndrome

	n (%) With a serum ALT >90th percentile		OR (95% CI)	
Maximum cTnI by quartiles	≥90th percentile (n=54)	<90th percentile (n=474)	Crude	Adjusted*
Quartile 1 (<0.60 μg/l)	4 (3.0)	128 (97.0)	1.00 (referent)	1.00 (referent)
Quartile 2 (0.61–7.48 μg/l)	7 (5.3)	125 (94.7)	1.79 (0.51 to 6.27)	0.58 (0.092 to 3.65)
Quartile 3 (7.5–49.9 μg/l)	6 (4.8)	119 (95.2)	1.61 (0.44 to 5.86)	1.74 (0.38 to 7.94)
Quartile 4 (>50.0 μg/l)	37 (26.6)	102 (73.4)	11.61 (4.00 to 33.64)	7.07 (1.83 to 27.37)

*Adjusted for age, sex, body mass index, serum creatinine, any plasma glucose, serum triglycerides, serum LDL-C, and chronic statin or other lipid-lowering agent use.

elevation of ALT ≥90th percentile using multinomial logistic regression analysis. Covariates included in the model were the same as for multiple linear regression analysis. A specificity analysis was repeated for the multinomial logistic regression analysis, in which the upper limit of ALT was set at 150 IU/l, thus excluding those with more severe forms of hepatitis.

Multinomial logistic regression analysis was also conducted to calculate crude and adjusted OR for the secondary outcomes in association with elevated ALT using the same covariates.

All listed variables were included in the models, a priori, and statistical significance was set at a two-sided p value less than 0.05. All analyses were performed using SAS V.8.0 (SAS Institute, Cary, North Carolina, USA).

RESULTS

A total of 1235 GRACE participants were admitted to St Michael's Hospital. Of these, 587 did not have an ALT measured within 5 days of hospitalisation, and another 120 did not meet the other inclusion criteria (table 1); hence, 528 persons were included in the current analysis. Those who did and did not have an ALT measured were comparable, for the most part, with the exception of a greater history of CVD and renal dysfunction, less aspirin but more lipid-lowering agent use, a higher rate of ST-segment elevation myocardial infarction at presentation, and more adverse outcomes arising after hospitalisation (table 1).

For the main study outcome, each 1 IU/l increase in ALT was independently associated with an increase in maximum cTnI of 0.16 μg/l (95% CI 0.10 to 0.22). An elevated ALT concentration >90th percentile was associated with a maximum cTnI concentration in the highest quartile, both in terms of the crude OR (11.61, 95% CI 4.00 to 33.64) and adjusted OR (7.07, 95% CI 1.83 to 27.37) (table 2). In the analysis restricted to those with an ALT concentration less than 150 IU/l, the crude, but not adjusted, OR for the highest quartile cTnI remained significant (appendix 1).

An elevated ALT >90th percentile was also associated with higher all-cause mortality, both in-hospital, as well as in-hospital and up to 6 months after discharge (table 3). The composite outcome of myocardial infarction, stroke, rehospitalisation or all-cause mortality was also associated with an elevated ALT (adjusted OR 2.71, 95% CI 1.12 to 6.56).

DISCUSSION

Among a select group of ACS patients, elevated serum ALT was significantly associated with more cardiac muscle injury, and poor clinical outcomes in-hospital and at 6 months.

The current study was limited to a single centre, and only a subset of patients had an ALT measured within 5 days of admission. While those who did undergo ALT measurement were somewhat comparable at baseline with those who did not, there were evident differences in the severity of underlying illness, initial presentation and the rate of adverse outcomes (table 1). Moreover, since ALT was measured after admission among some participants, a higher concentration may have been a product of severe heart failure or medication use, even though attempts to control for the latter were undertaken. When we restricted our sample to those with an ALT less than 150 IU/l, non-significant effects were seen for maximum measured cTnI. Finally, although serum ALT is a sensitive marker for NAFLD, it lacks specificity, especially in the acute care setting.[6–8] We chose to use ALT rather than ultrasound imaging of the liver because imaging was not available for most participants, and ALT is easily measured at a lower cost. Clearly, MRI or ultrasound characterisation and/or quantification of fatty liver soon after presentation would improve upon these limitations.

The impact of NAFLD in the setting of ACS has not been studied to date, but there is consistent evidence linking NAFLD to coronary artery disease and acute stroke (table 4). Insulin resistance—a major driving force for atherogenic dyslipidemia—contributes to the pathogenesis of NAFLD.[1 19] Hepatic and systemic inflammation in NAFLD may lead to the release of proatherogenic factors from the liver mediated by the nuclear factor-κB pathway.[1 14] Adipokine originating from adipose tissue may further amplify this inflammatory cascade by stimulating hepatic release of C-reactive protein, an established risk factor for CVD.[20]

It is premature to suggest that ALT be measured as a predictive marker in persons with ACS. The degree to which ALT

Table 3 Association between serum alanine aminotransferase (ALT) and adverse outcomes following hospital admission for suspected acute coronary syndrome

	n (%) With a serum ALT ≥90th percentile		OR (95% CI)	
Outcome	≥90th percentile (n=54)	<90th percentile (n=474)	Crude	Adjusted*
All-cause mortality, in-hospital	28 (51.9)	44 (9.3)	10.55 (5.69 to 19.56)	10.84 (3.63 to 32.38)
All-cause mortality, in-hospital and up to 6 months after discharge	28 (51.9)	52 (10.9)	8.76 (4.78 to 16.07)	8.96 (3.28 to 24.49)
Composite of myocardial infarction, stroke, rehospitalisation or all-cause mortality up to 6 months	33 (67.3)	107 (32.9)	4.20 (2.22 to 7.97)	2.71 (1.12 to 6.56)

*Adjusted for age, sex, body mass index,, serum creatinine, any plasma glucose, serum triglycerides, serum LDL-C, and chronic statin or other lipid-lowering agent use.

Table 4 Published studies of the risk of cardiovascular disease (CVD) or related mortality associated with non-alcoholic fatty liver disease (NAFLD) or an elevated alanine aminotransferse (ALT)

Year (reference)	Study design	Total participants analysed (n)	Baseline method of assessment of NAFLD	Cardiovascular disease study outcome	Adjusted risk (95% CI) for study outcome comparing presence versus absence of NAFLD
2006[14]	Cross-sectional analysis	7526	Elevated serum ALT >43 IU/l	10-y coronary heart disease (CHD) risk by Framingham Risk Score	• adjusted HR men 1.3 (1.2 to 1.5)
2007[6]	Prospective cohort study	1439	Upper tertileserum ALT	• 10-y all-cause mortality	• HR women 2.1 (1.5 to 3.0)
				• Fatal and non-fatal CVD	• HR 1.3 (0.92 to 1.8)
				• Fatal and non-fatal CHD	• HR 1.4 (1.1 to 1.8)
					• HR 2.0 (1.4 to 3.1)
2005[15]	Prospective nested case-control study	744	Ultrasound findings of hepatic steatosis	Incidence of CVD event within 5-year follow-up in patients with DM2	OR 1.6 (1.2 to 1.9)
2007[16]	Prospective observational cohort study	1221	Ultrasound findings of hepatic steatosis	Incidence of CVD within a 5-year follow-up without DM2	OR 4.1 (1.6 to 10.8)
2008[17]	Prospective cohort study	37085	Elevated serum ALT >31 IU/l	CVD- or diabetes-related mortality	RR 2.3 (1.0 to 5.1)
2011[18]	Cross-sectional study	303	Elevated serum ALT ≥95th centile	Acute ischemic stroke	OR 3.3 (1.3 to 8.4)
Current	Prospective cohort study	528	Elevated serum ALT ≥90th centile	• Maximum measured cardiac troponin concentration at 24 h	• OR 7.1 (1.8 to 27.4)
				• All-cause mortality in-hospital	• OR 10.8 (3.6 to 32.4)
				• All-cause mortality in-hospital and ≤6 months	• OR 9.0 (3.3 to 24.5)
				• Composite of myocardial infarction, stroke, re-hospitalisation or all-cause mortality ≤6 months	• OR 2.7 (1.1 to 6.6)

CHD, coronary heart disease; CVD, cardiovascular disease; DM2, type 2 diabetes mellitus; RR, adjusted relative risk.

improves predictive models of prognosis warrants further study. Optimally, ALT could be measured in parallel with imaging of the liver.

CONCLUSION

NAFLD, determined by an elevated serum ALT, is associated with a higher risk of adverse outcomes in persons with ACS. It remains to be determined if NAFLD is an independent prognostic marker among persons with ACS.

Contributors LR: study conception, design and analysis, drafting of manuscript, manuscript revision, approval of final version; JGR: study conception, design and analysis, drafting of manuscript, manuscript revision, approval of final version; SGG: design and analysis, manuscript revision, approval of final version; ATY: design and analysis, manuscript revision, approval of final version; AM: design and analysis, manuscript revision, approval of final version.

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