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Association between plasma lipid levels during acute coronary syndrome and long-term malignancy risk. The ABC-4* study on heart disease

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Abstract

Background: Emerging evidence suggests that patients with coronary artery disease carry an increased risk of developing malignancy, with deleterious effects on long-term prognosis. Our aim was to ascertain whether baseline plasma lipid levels during acute coronary syndrome (ACS) are associated with malignancy in long-term.

Methods: This study included 589 patients admitted with ACS to three centers and discharged alive. Plasma lipid levels were assessed on the first morning after admission. Patients were followed for 17 years or until death.

Results: Five hundred seventy-one patients were free from malignancy at enrollment, of them 99 (17.3%) developed the disease during follow-up and 75 (13.1%) died due to it. Compared to patients without malignancy, those with malignancy showed lower plasma levels of total cholesterol (TC), low-density lipoprotein (LDL), and triglycerides (TG). The groups showed similar statin use rates at any time in follow-up. The incidence rate of neoplasia and neoplastic mortality was higher in patients with baseline TC or LDL values ≤ median; they showed 85 and 72% increased incidence rate of developing malignancy and 133 and 122% increased incidence rate of neoplastic death respectively. No differences were observed relative to HDL and TG levels. In survival analysis using Cox regression with parsimonious models, patients with baseline TC or LDL values > median, respectively, showed risks of 0.6(95% CI 0.4–0.9; $p = 0.01$) and 0.6(95%CI 0.4–0.9; $p = 0.02$) for malignancy onset, and 0.5(95% CI 0.3–0.8; $p = 0.005$) and 0.5(95% CI 0.3–0.8; $p = 0.004$) for neoplastic death. Similar results were obtained using competitive risk analysis with parsimonious models.

Conclusions: This long-term prospective study of an unselected real-world patient sample showed that neoplasia onset and mortality are independently associated with low plasma TC and LDL levels at admission for ACS.

Keywords: Acute coronary syndrome, Coronary artery disease, Neoplasia, Plasma lipids, Long-term follow-up, Competitive risks

Background

Cardiovascular disease (CVD) and cancer are the two main causes of mortality worldwide [1, 2]. Most investigations of prognosis following acute coronary syndrome (ACS) focus on cardiovascular events, and few examine long-term fatalities [3, 4]. However, emerging evidence suggests that patients affected by CVD, particularly coronary artery disease (CAD), carry an increased risk of cancer development, which has a deleterious effect on long-term prognosis [5, 6]. It is not yet understood which patients have this higher risk of cancer.

Several studies indicate that cancer risk and cancer-related mortality show an inverse relationship with plasma levels of total cholesterol (TC) and low-density lipoprotein (LDL) in the general population [7–13].To our knowledge, this relationship has not been investigated in patients with ACS.ACS is reportedly accompanied by substantial transient changes

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in the plasma lipid profile, including increases of plasma triglycerides (TG) and very low-density lipoproteins, and decreases of TC, high-density lipoprotein (HDL), and LDL levels [14, 15]. Notably, a 10% decrease in TC has been described [15], which is clinically significant and warrants measurement of serum lipids in patients with acute myocardial infarction (AMI) within the first hours after presentation.

In the present study, we investigated the possible association between plasma lipid profile during ACS (admission plasma lipid level) and the subsequent long-term cancer risk over 17 years of follow-up in an unselected sample of patients discharged alive after an index hospitalization with ACS.

Methods

Patients

The ABC Study on Heart Disease is an ongoing prospective investigation designed to represent, as closely as possible, an unbiased population of patients with ACS (www.abcstudy.foundation). The cohort includes Caucasian patients with definite ACS—including ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction(NSTEMI), or unstable angina—who were admitted to the intensive care units of the Adria, Bassano and Conegliano hospitals between June 1995 and January 1998. The original aim of the ABC study was to monitor these patients with regards to natural long-term history and to evaluate both non-fatal and fatal events, and causes of death. Another study aim was to investigate the prognostic value of multiple baseline clinical variables. Criteria for ACS diagnosis included the clinical presentation, electrocardiogram findings, and the presence of serum biochemical markers of necrosis [16, 17].

A total of 741 patients were considered eligible upon admission of whom 84 were excluded because they had diseases other than ACS, and 23 were excluded due to a lack of baseline data. Among the 634 enrolled patients with ACS, 45died during the index hospitalization; hence, the post-discharge follow-up study included 589 patients (Fig. 1). Malignant neoplasia had already been diagnosed in 19 patients at the time of enrollment, one of whom died during the index hospitalization. Each patient received an anonymous code, and no personal data or identifiers were included in the baseline or follow-up database. All enrolled patients gave their written informed consent, and the study was approved by each hospital ethics committee.

Measurements and follow-up

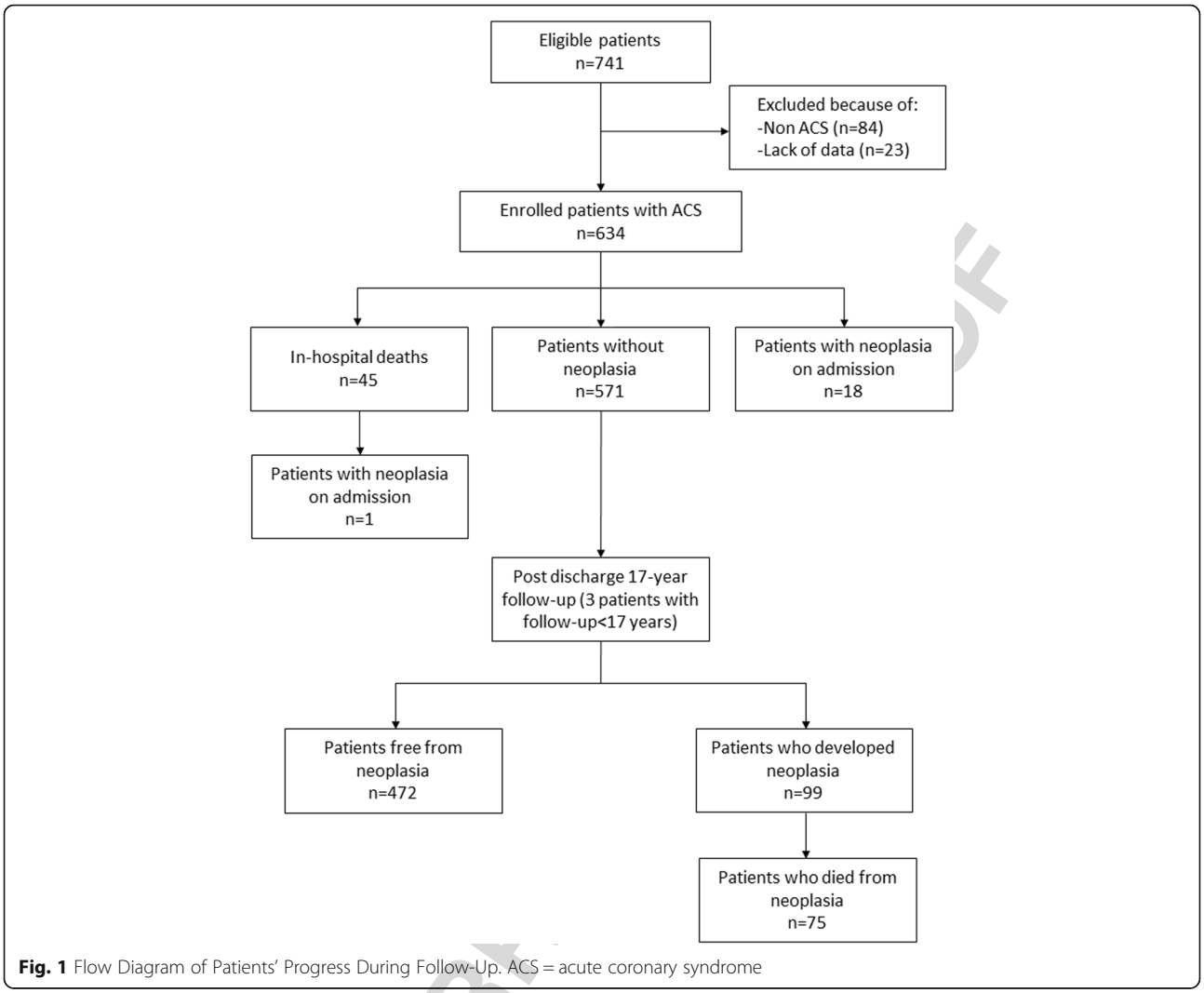
At enrollment, thorough patient history was collected from medical records and patient interviews. All presently analyzed baseline clinical and laboratory data were obtained during the first 7 days of hospitalization in the intensive coronary care unit. ACS diagnosis criteria were the fulfillment of at least two of the following: central chest pain lasting > 30 min; typical changes in serum enzymes, including total creatine kinase (CK) and creatine kinase MB (CK-MB); and typical electro-cardiogram changes with pathological Q waves and/or localized ST-T changes in at least two contiguous leads [18]. Within 12 h after admission, a fasting venous blood sample was drawn for TC, LDL, HDL measurements. LDL concentrations were estimated using the modified Friedewald formula (MFF): LDL (mg/dL) = Non-HDL × 90% – TG × 10% [19]. In all three hospitals, plasma lipid measurement was performed using an enzymatic colorimetric method [20]. Details of the measured variables have been previously published [16, 17].

Each patient underwent a clinical check-up at 1, 3, 5, 7, 10, 12, 15, and 17 years after recruitment. At each recruitment hospital, two cardiologists were responsible for monitoring the cohort of patients throughout the follow-up. Data were obtained from scheduled examinations, public administrations, hospital records, family doctors, post-mortem examinations, and death certificates.

For the present study, the following data were recorded: presence of malignant neoplastic disease at the index admission; incidence of neoplastic disease and time of onset, i.e., the first documented clinical diagnosis of the disease; and time of death due to any cause. All patients were followed for 17 years or until the time of death. All data after enrollment were prospectively recorded following the protocol of the ABC Study on Heart Disease. By protocol, baseline data and follow-up data were recorded in two different data sheets. For the present analysis, the datasheets were merged after completion of 17 years of follow-up.

Statistical analysis

The accrued variables were analyzed as continuous variables or proportions. Log transformations were applied to correct for positively skewed distributions, as appropriate. We analyzed measured variables using the unpaired Student's t-test, and categorical variables using Pearson's chi-square test. If a patient dropped out prior to 17 years of follow-up, her/his data were censored at that time. Survival curves were constructed using cumulative incidence as a function of neoplasia onset and neoplasia-related death [21]. We compared cumulative incidences using the Pepe and Mori Test [22] and incidence rates using Mantel-Haenszel estimates of the rate ratio. We analyzed the times from enrollment (i.e., admission for ACS) to the onset of neoplastic disease and to death using Cox proportional hazard regression analysis, as well as with competitive risk regression analysis using the Fine-Gray method [23]. Scaled Schoenfeld residuals were used to test the proportionality assumption



f1.1 f1.2 **Fig. 1** Flow Diagram of Patients' Progress During Follow-Up. ACS = acute coronary syndrome

with 95% confidence intervals (CI). All hazard ratios (HR) estimated in survival analysis were based on analysis of dichotomous variables, using the 50th percentile for continuous variables, and absence/presence of a feature for categorical variables. The same models were also assessed using the continuous baseline variables, and the strength of association expressed as Z values (the ratio of the HR and SE). The International System of Units is used throughout the text. Unless otherwise indicated, two-tailed P values of < 0.05 were considered significant. Statistical analyses were performed using STATA 14 (College Station, Texas, USA).

Results

All enrolled patients completed the follow-up unless pre-empted by death—except three patients for whom survival time was censored before 17 years (two withdrew consent and one moved overseas). Among the589 patients who were discharged alive, 18patients had previously diagnosed malignancy at the time of enrollment and were excluded from the present analysis. Ninety-nine patients developed the disease during the follow-up (Fig. 1). Table 1 **T1** presents the patients' baseline clinical characteristics according to the development of neoplasia during follow-up. The two groups did not differ in age at enrollment, history of hypertension or alcohol use. The prevalence of neoplasia was higher among males. Patients with neoplasia were more frequently smokers, and less frequently had diabetes or baseline signs of heart failure. Regarding humoral characteristics, patients with neoplasia had lower plasma levels of peak lactate dehydrogenase (LDH), TC, LDL, and TG. Plasma HDL levels did not differ between groups. The rate of using lipid-lowering treatment throughout follow-up did not significantly differ between non-neoplastic patients (47%) and neoplastic patients (43%)($chi^2 = 2.9$, $p = 0.23$).

Comparing patients who developed neoplasia to those who did not, there were no differences in the rate of

t1.1 **Table 1** Baseline characteristics of patients with acute coronary syndrome by developing the neoplastic disease during follow-up

t1.2 Variable	Overall sample ($n = 571$)	Non neoplastic ($n = 472$)	Neoplastic ($n = 99$)	*P* values
t1.3 Median age. Years	67 (58–74)	67 (58–75)	67 (61–74)	0.71
t1.4 Gender (female)	30	31	21	0.04
t1.5 Education (above primary school)	26	26	26	0.93
t1.6 Median body mass index. kg/m2	26 (24–28)	26(24–28)	25(24–29)	0.66
t1.7 Smoking habit [a]	67	65	80	0.003
t1.8 Alcohol use	74	74	74	0.99
t1.9 Hypertension	48	48	46	0.66
t1.10 Diabetes mellitus	23	25	13	0.01
t1.11 Median systolic blood pressure. mmHg	120 (110–130)	120 (110–130)	120 (110–130)	0.62
t1.12 Median diastolic blood pressure. mmHg	80 (70–80)	76 (70–80)	80 (70–80)	0.10
t1.13 Median heart rate. Beats/min	71(60–82)	72 (63–82)	70 (60–80)	0.07
t1.14 non-ST elevation ACS	38	37	46	0.09
t1.15 KIllip class > 1	66	36	22	0.008
t1.16 LVEF ($n = 500$)	52 (45–60)	52 (45–60)	56 (46–61)	0.06
t1.17 Hb (g/L)	137 (125–147)	137 (126–147)	137 (126–147)	0.88
t1.18 Blood glucose level (mmol/L)	6.7(5.6–8.8)	6.8 (5.7–9.3)	6.2 (5.4–7.7)	0.05
t1.19 Serum creatinine level (mmol/L)	0.08 (0.07–0.1)	0.08 (0.07–0.1)	0.08 (0.07–0.09)	0.06
t1.20 CK-MB peak (U/L)[b]	103(43–205)	106(43–207)	78(34–186)	0.15
t1.21 LDH peak (U/L)[b]	848(517–1380)	874(538–1418)	701(454–1200)	0.003
t1.22 Serum lipids (mmol/L)[b]				
t1.23 Total cholesterol	5.4(4.6–6.3)	5.5 (4.7–6.3)	5.2(4.4–6.2)	0.01
t1.24 LDL cholesterol[c]	3.4(2.8–4.1)	3.5 (2.8–4.1)	3.3(2.6–4.0)	0.03
t1.25 HDL cholesterol	1.1(1.0–1.3)	1.1 (1.0–1.3)	1.1(1.0–1.3)	0.73
t1.26 Triglycerides	1.4(1.0–2.0)	1.5 (1.1–2.1)	1.3(0.9–1.9)	0.02

t1.27 *ACS* Acute coronary syndrome, *CK-MB* Creatine kinase-MB isoenzyme, *HDL* High density lipoproteins, *LDH* Lactate dehydrogenase-1 isoenzyme, *LDL* Low density
t1.28 lipoproteins, *LVEF* Left ventricular ejection fraction, *Hb* Hemoglobin
t1.29 The values are presented as medians and interquartile ranges or percentages
t1.30 [a]Previous smokers and currently smoking patients
t1.31 [b]*p* values were calculated on log-transformed data
t1.32 [c]Calculated using modified Friedewald formula
t1.33 For Hemoglobin: 1 g/L = 0.1 g/dl
t1.34 For Glucose: 1 mmol/l = 18.01 mg/dl
t1.35 For total cholesterol: LDL and HDL: 1 mmol/l = 38.66976 mg/dl
t1.36 For Triglycerides: 1 mmol/l = 88.57396 mg/dl

191 revascularization; the rate of PCI was (17 and 21%
192 respectively; $chi^2 = 0.66$, $p = 0.42$) and of CABG was
193 (17 and 20% respectively;$chi^2 = 0.34$, $p = 0.56$).

194 The incidence rate of new malignancy throughout
195 follow-up after ACS was approximately18 cases/1000
196 person-years. Unexpectedly, this incidence rate was
197 markedly higher (23 cases/1000 person-years)among
198 patients with baseline TC ≤ median value of 208 mg/dL,
199 and the estimated rate ratio was significantly below 1
T2 200 (Table 2). A similar rate ratio was observed for LDL. In
201 contrast, the rate ratio was closer to 1and non-significant
202 for HDL and TG.

203 At the end of follow-up, 75 (13.1%) patients had died
204 due to neoplasia;(67 patients, died directly due to neo-
205 plasia,4 patients had concomitant non-cardiovascular
206 adverse events likely contributing to death, and 4
207 patients had concomitant cardiovascular adverse events
208 likely contributing to death). However, in the present
209 analysis, we considered all the 75 patients died with
210 malignancy as a single class of patients. The incidence
211 rate approximated13 cases/1000 person-years. Among
212 patients with TC ≤ median plasma values, the incidence
213 rate was more than double of that observed among
214 patients with TC > median value and the estimated rate
215 ratio was highly significantly different (Table 2). Similar
216 results were observed for LDL, while no significant
217 differences were observed for HDL and TG (Table 2).

218 Overall, patients with TC or LDL baseline values
219 > median value, had an increase of 85 and 72% in
220 malignancy onset and 133 and 122% increase in neoplastic

t2.1 **Table 2** Incidence Rate of Neoplasia Onset, mortality and Comparison of Cumulative Incidence According to Lipid Levels

t2.2 / t2.3 Variable	Person-years	Incidence rate/1000 person-years	Mantel-Haenszel estimates of rate ratio			Percent relative effect (%)	Pepe Mori cumulative incidence comparison	
			RR	X^2	*p value*		X^2	*p* value
t2.4 Neoplasia onset after ACS (n = 99)	5544							
t2.5 Total cholesterol								
t2.6 ≤ Median		23	0.54	8.8	0.003	85	7.4	0.006
t2.7 > Median		13						
t2.8 LDL cholesterol								
t2.9 ≤ Median		23	0.58	7.1	0.007	72	4.6	0.03
t2.10 > Median		13						
t2.11 HDL cholesterol								
t2.12 ≤ Median		17	1.10	0.2	0.63	−9	0.2	0.63
t2.13 > Median		19						
t2.14 Triglycerides								
t2.15 ≤ median		20	0.75	2.0	0.16	33	2.5	0.11
t2.16 > median		15						
t2.17 Neoplasia-related death after ACS (*n* = 75)	5877							
t2.18 Total cholesterol								
t2.19 ≤ Median		18	0.43	12.1	0.0005	133	10.7	0.001
t2.20 > Median		8						
t2.21 LDL cholesterol								
t2.22 ≤ Median		18	0.45	11.4	0.0007	122	7.8	0.005
t2.23 > Median		8						
t2.24 HDL cholesterol								
t2.25 ≤ Median		11	1.33	1.6	0.8	−25	0.5	0.47
t2.26 > Median		15						
t2.27 Triglycerides								
t2.28 ≤ Median		15	0.68	2.7	0.09	47	1.6	0.20
t2.29 > Median		11						

t2.30 *ACS* Acute coronary syndrome, *HDL* High-density lipoproteins, *LDL* Low-density lipoproteins

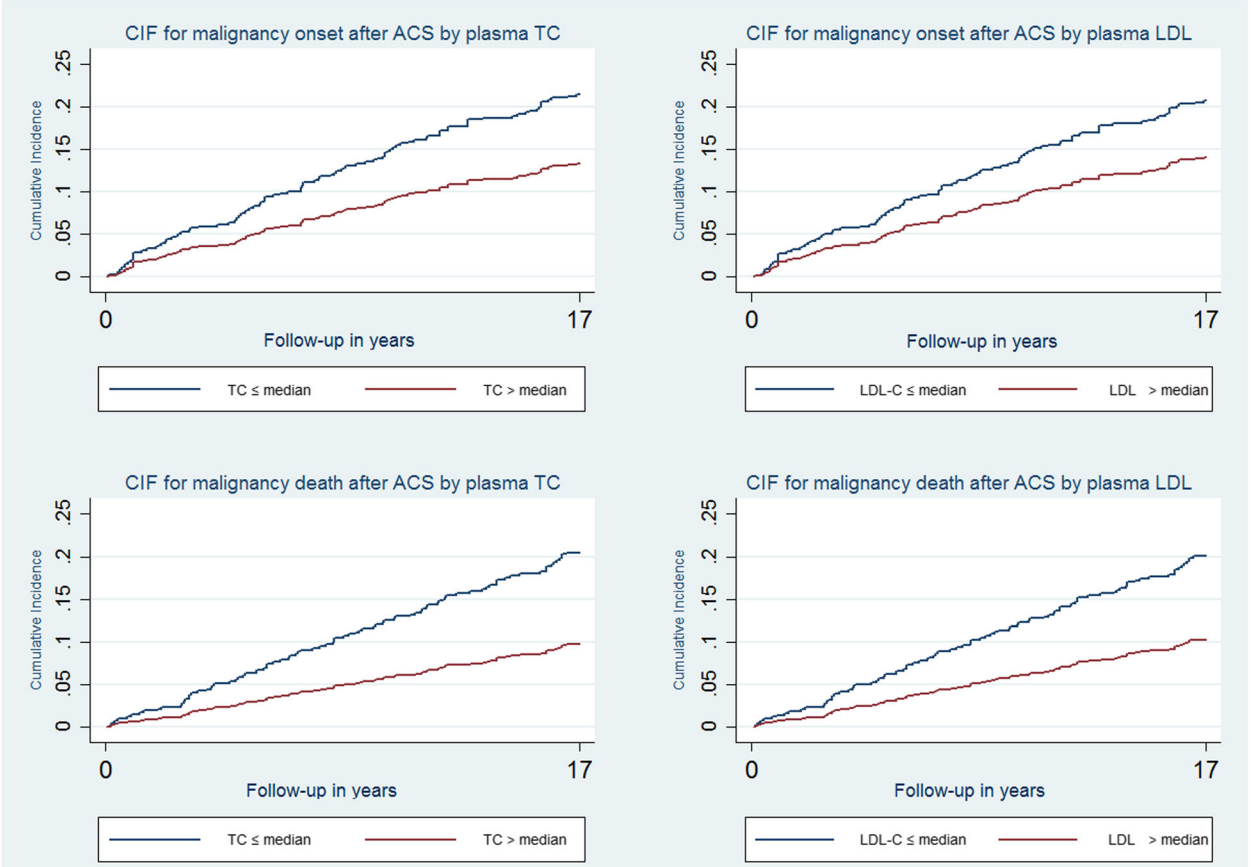
mortality, respectively, as compared to the patients with TC or LDL baseline values ≤median value.

F2 Figure 2 presents the cumulative incidence of malignancy onset and neoplastic death throughout the follow-up in patients with plasma TC and LDL values of > or ≤ median values, revealing significant differences between these groups (Table 2). There were no significant differences F3 relative to HDL and TG (Fig. 3).

Univariable Cox survival analysis demonstrated that the hazard of malignancy onset and neoplastic mortality throughout follow-up after ACS were higher among patients with baseline TC or LDL values ≤ median values T3 (Table 3). The proportional hazards assumption was verified for all variables concerning plasma lipid levels ($p \geq 0.10$).

The higher hazard remained significant even after accounting for clinical confounders in the fully adjusted models and the parsimonious models (Table 3). Fully adjusted models included age, gender, body mass index, smoking habit, diabetes mellitus, hypertension, baseline in-hospital heart failure, Q-wave myocardial infarction, lipid-lowering treatment with statins, and hospital site. The proportional hazards assumption was also not violated for all lipids and for all other variables in the fully adjusted model ($p \geq 0.10$), except for the presence of diabetes ($p < 0.01$).

The final survival analysis accounted for competitive risks (malignancy risk versus all other causes of death) and showed very similar results, both in univariable analysis and in the fully adjusted and parsimonious models (Table 3).The fully adjusted model showed that onset of malignancy was associated with smoking and HF at admission, the risks were 2.2(95% CI 1.2–4.1; $p = 0.02$) and 0.6(95% CI 0.3–1.0; $p = 0.03$) respectively, while the



f2.1 **Fig. 2** Cumulative Incidence Rate of Malignancy Onset and Neoplastic Death According to TC and LDL Values. ACS = acute coronary syndrome;
f2.2 CIF = denotes cumulative incidence function; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol
f2.3

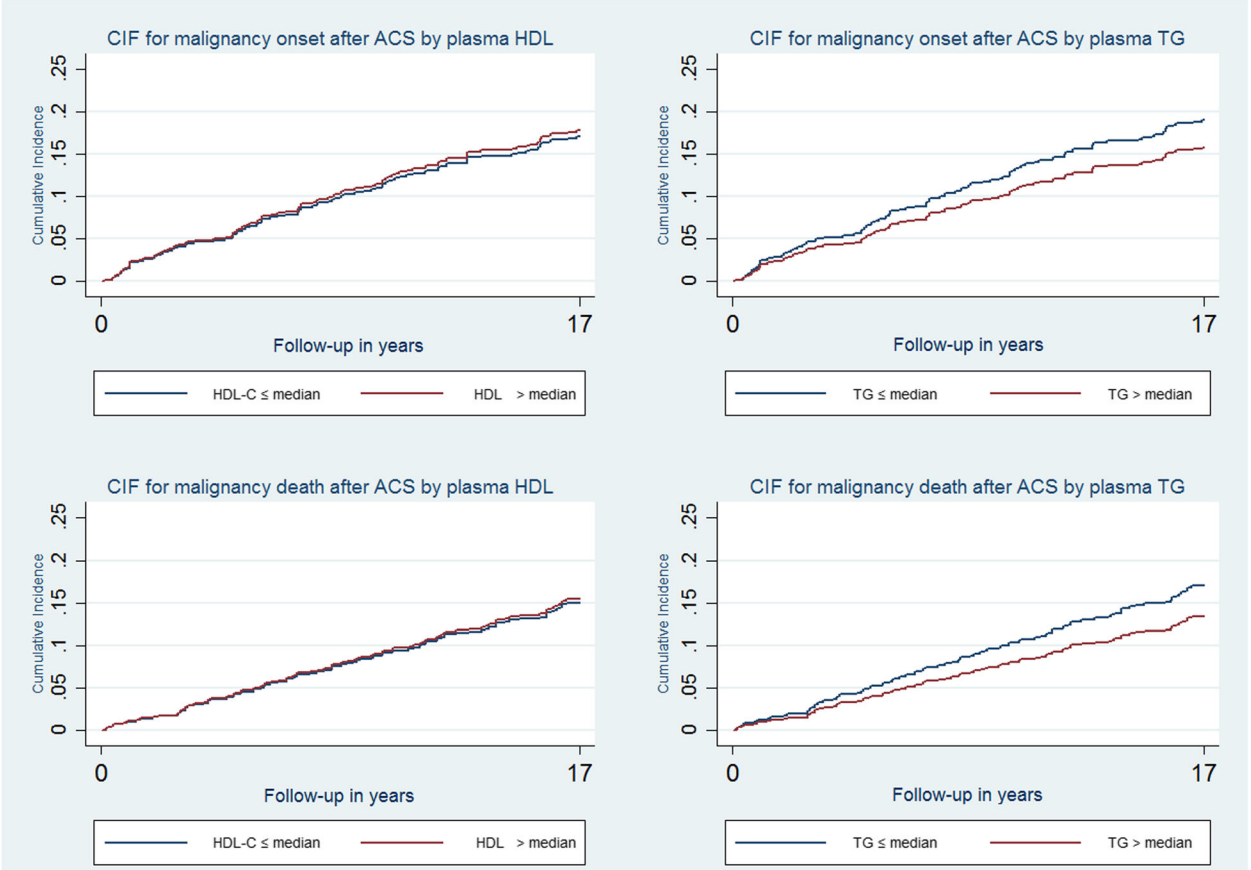
risks for neoplastic mortality were 2.5(95% CI 1.5–3.9; $p = 0.00$), 2.3(95% CI 1.3–4.3; $p = 0.01$) and 0.6(95% CI 0.4–1.0; $p = 0.06$) for age, smoking habits and HF at admission respectively. Possible interactions for TC and LDL were tested versus important baseline clinical variables(age, gender, the presence of hypertension, diabetes mellitus, smoking habit), revealing no interactions with any variables included in the fully adjusted model.

Discussion

The results of this prospective study, virtually without drop-out patients, showed an independent higher risk of malignancy onset and mortality among patients with low TC and LDL values upon hospital admission for ACS. In the present analysis, all the patients were free of malignancy at enrollment. These results were consistent for both malignancy onset and mortality through 17 years of follow-up, and independent from important baseline clinical confounders, including age, gender, hypertension, diabetes mellitus, smoking habits, type of ACS, and heart failure. Furthermore, lipid-lowering treatment did not seem to influence the relationship of TC and LDL with cancer onset and mortality, with neoplasia incidence rates were similar between patients who did and did not receive statin medication during follow-up. Moreover, survival analysis controlling for lipid-lowering treatment during follow-up (both Cox regressions and competitive risks regressions) confirmed that the association was independent of the treatment.

Cancer and CVD are highly complex phenotypes and their concurrence is a controversial issue given the competing risks of mortality [24]. While inflammation and oxidative stress appear to be major unifying factors in the etiology and progression of both diseases, emerging evidence suggests that modifiable risk factors including unhealthy diet, sedentary lifestyle, obesity, and tobacco smoking are central to the pathogenesis of both diseases and are reflected in common genetic, cellular, and signaling mechanisms which have been thoroughly discussed [25–27].

Considering the dramatic prognostic severity of these clinical conditions, it is critical that we improve our understanding of this important biological overlap. Many observational cancer epidemiology studies showed that



f3.1 **Fig. 3** Cumulative Incidence Rate of Malignancy Onset and Neoplastic Death According to HDL And TG Values. ACS = acute coronary syndrome;
f3.2 CIF = cumulative incidence function; HDL-C = High density lipoprotein cholesterol; TG = Triglycerides
f3.3

low cholesterol concentrations are associated with a significantly increased risk of total cancer and cancer-related mortality [7–13]although not all data support this relationship [28, 29].Regarding the possible explanations of this inverse association, authors suggest a direct causal link [30] while others discuss the possible effects of preclinical cancer [7].Other postulations include changes in cell membrane fluidity that lead to neoplastic transformation, reduced tumor immunogenicity secondary to membrane cholesterol loss, altered levels of fat-soluble antioxidants or vitamins transported in LDL particles, protective effects of LDL against lymphocyte activation, and virally induced cell transformation and genetic factors [30].

The relationship between plasma cholesterol concentration and mortality is complex. Although plasma concentration is positively correlated with CAD-related mortality, it shows a negative relationship with death from cancer. These two relationships could reflect causal mechanisms that are reversible by changes in plasma TC concentration. In this scenario, the benefits of lipid reduction for heart disease might be partly offset by increased cancer-related mortality [31].

In concordance with the medical knowledge, we found association between malignancy risk and other important variables as age and smoking, while interestingly the higher levels of cholesterol and LDL were consistently associated with lower malignancy risk.

Another important issue is how statin treatment during follow-up influences outcomes. The relationship between statin treatment and malignancy is controversial, as some studies report that statin-treated patients carry an increased risk of cancer in certain body segments [32-34], other studies report that statin treatment conveys a protective effect [35, 36] and several meta-analyses and observational studies have identified no association between statin use and overall cancer risk [37–43]. In a recent comprehensive review, the authors. Concluded that statin use seems to be safe in relation to cancer risk but that a preventive effect is not yet established [44].In our patient sample, statin treatment did not seem to have a significant influence on neoplastic

t3.1 **Table 3** Cox Regression and Competitive Risks Analysis for Neoplasia Onset and mortality after Acute Coronary Syndrome

t3.2 Variable	Univariable analysis			Multivariable analysis					
t3.3				(fully adjusted model)[a]			(parsimonious model)		
t3.4 t3.5	Hazard ratio (95% CI)	Z value	*p* value	Hazard ratio (95% CI)	Z value	*p* value	Hazard ratio (95% CI)	Z value	*p* value
t3.6 Cox regression survival analysis									
t3.7 Neoplasia onset (n = 99)									
t3.8 Above median TC	0.6(0.4–0.8)	−2.9	0.003	0.6(0.4–0.9)	− 2.3	0.02	0.6(0.4–0.9)[b]	−2.6	0.01
t3.9 Continuous TC		−3.6	< 0.0001		−3.0	0.003		−2.3[c]	0.002
t3.10 Above median LDL-C	0.6(0.4–0.9)	− 2.6	0.009	0.6(0.4–0.9)	−2.0	0.04	0.6(0.4–0.9)[b]	−2.3	0.02
t3.11 Continuous LDL-C		−3.2	0.001		−2.5	0.01		−2.8[c]	0.006
t3.12 Above median HDL-C	1.1(0.7–1.6)	0.5	0.63	1.0(0.7–1.5)	−0.1	0.94	1.0(0.7–1.5)[c]	−0.1	0.89
t3.13 Continuous HDL-C		0.03	0.74		−0.7	0.50		−0.3[c]	0.80
t3.14 Above median TG	0.8(0.5–1.1)	−1.4	0.15	0.8(0.5–1.2)	−1.1	0.26	0.8(0.6–1.2)[c]	−0.9	0.35
t3.15 Continuous TG		−3.0	0.003		− 2.1	0.03		−2.1[c]	0.04
t3.16 Neoplasia-related death (n = 75)									
t3.17 Above median TC	0.4(0.3–0.7)	−3.4	0.001	0.5(0.3–0.9)	−2.3	0.02	0.5(0.3–0.8)[b]	−2.8	0.005
t3.18 Continuous TC		−4.3	< 0.001		−3.3	0.001		−3.7[c]	< 0.001
t3.19 Above median LDL-C	0.4(0.3–0.7)	−3.2	0.001	0.5(0.3–0.9)	−2.4	0.02	0.5(0.3–0.8) [b]	−2.9	0.004
t3.20 Continuous LDL-C		−4.3	< 0.001		−3.3	0.001		−3.6[c]	< 0.001
t3.21 Above median HDL-C	1.3(0.9–2.1)	1.3	0.20	1.1(0.7–1.8)	0.4	0.66	1.1(0.7–1.7)[c]	0.4	0.67
t3.22 Continuous HDL-C		0.9	0.37		−0.1	0.91		0.21[c]	0.83
t3.23 Above median TG	0.7(0.4–1.0)	−1.6	0.10	0.8(0.5–1.3)	−0.8	0.43	0.8(0.5–1.3)[c]	−0.9	0.37
t3.24 Continuous TG		−3.0	0.003		−1.7	0.09		−1.8[c]	0.06
t3.25 Competitive risks survival analysis									
t3.26 Neoplasia onset (n = 99)									
t3.27 Above median TC	0.6(0.4–0.9)	−2.6	0.01	0.6(0.4–0.9)	−2.4	0.02	0.6(0.4–0.9)[d]	−2.5	0.01
t3.28 Continuous TC		−2.5	0.01		−2.6	0.01		−2.7	0.008
t3.29 Above median LDL-C	0.7(0.4–0.9)	−2.1	0.04	0.6(0.4–0.9)	−2.0	0.04	0.7(0.4–0.9)[d]	−2.1	0.04
t3.30 Continuous LDL-C		−2.3	0.02		−2.3	0.02		−2.4	0.02
t3.31 Above median HDL-C	1.1(0.7–1.6)	0.2	0.82	1.0(0.7–1.5)	0.1	0.95	1.0(0.7–1.5)[d]	0.2	0.84
t3.32 Continuous HDL-C		0.4	0.69		−0.1	0.93		0.3	0.79
t3.33 Above median TG	0.8(0.5–1.2)	−1.0	0.30	0.8(0.5–1.3)	−0.9	0.36	0.8(0.5–1.2)[d]	−1.2	0.25
t3.34 Continuous TG		−2.4	0.01		−2.4	0.02		−2.6	0.01
t3.35 Neoplasia-related death (n = 75)									
t3.36 Above median TC	0.5(0.3–0.8)	−3.1	0.002	0.5(0.3–0.9)	−2.5	0.01	0.5(0.3–0.8)[d]	−2.9	0.003
t3.37 Continuous TC		−3.2	0.001		−2.8	0.006		−3.3[d]	0.001
t3.38 Above median LDL-C	0.5(0.3–0.8)	−2.8	0.005	0.6(0.3–0.9)	−2.3	0.02	0.5(0.3–0.8)[d]	−2.7	0.007
t3.39 Continuous LDL-C		−3.3	0.001		−2.7	0.007		−3.3[d]	0.001
t3.40 Above median HDL-C	1.3(0.8–2.0)	1.0	0.32	1.2(0.8–1.9)	0.8	0.44	1.3(0.8–2.0)[d]	1.0	0.32
t3.41 Continuous HDL-C		1.0	0.31		0.5	0.60		0.9[d]	0.35
t3.42 Above median TG	0.7(0.5–1.2)	−1.3	0.19	0.8(0.5–1.3)	−0.8	0.41	0.7(0.5–1.1)[d]	−1.4	0.16
t3.43 Continuous TG		−2.6	0.008		−2.1	0.04		−2.8[d]	0.006

t3.44 *ACS* Acute coronary syndrome, *CI* Confidence interval, *HDL* High-density lipoproteins, *LDL* Low-density lipoproteins
t3.45 [a]Adjusted for age, gender, BMI, smoking, diabetes mellitus, hypertension, in-hospital HF, Q-wave myocardial infarction, statin therapy, and hospital
t3.46 [b]Adjusted for age, smoking, and Q-wave myocardial infarction
t3.47 [c]Adjusted for age and smoking
t3.48 [d]Adjusted for smoking and in-hospital HF

onset or neoplastic death. The rates of neoplastic onset and death were similar between patients with and without treatment throughout follow-up. In the multivariable survival models, including those dealing with competitive risks assessment, statin treatment did not modify the association between plasma lipid levels and outcomes. Sub-analysis was performed among our patients who never received statin treatment throughout the entire study period, and the results support the hypothesis that the negative association between low admission plasma lipid levels (TC and LDL) is independent of treatment.

Study limitations

A major limitation of the ABC study of ACS was that at the time of patient enrollment, percutaneous coronary angioplasty was not yet used to reopen coronary arteries in patients with STEMI. Thus, it remains uncertain whether the results might have been altered by early mechanical reperfusion. However, Cordero and his collogue reported recently that more than 86% of their patients have been subjected to revascularization post ACS and there were no differences in the revascularization rate among patients who did or didn't develop neoplasia during the 7-year follow up [5]. Additionally, statin treatment was much less commonly used at the beginning of the study period (1995–1998), and steadily increased from the 1st to the 17th year of follow-up, in accordance with guideline revisions over the time period. However, our statistical analysis results suggested that lipid-lowering treatment did not influence the association of plasma lipid levels with cancer onset and mortality. Yet is to be considered that risk factors of occurrence of cancer vary by type of cancer, and it is of clinical relevance. However, this issue is beyond the scope of the present study, which aimed to assess the relationship between lipid and cancer incidence and death after ACS. One more limitation is that only baseline plasma lipid measurements were considered in the present study, while changes in lipid profile are to be expected through such a long time of follow up, mainly due to lifestyle and treatment changes. Nevertheless, the associations we observed seem to be clinically consistent, and the assessment of lipid profile at admission for ACS can be a sort key point in the patient's life. Finally, since the patients in this study were all Caucasians, we cannot generalize the present findings to other populations and ethnic groups.

Conclusions

This long-term prospective study of an unselected real-world patient sample showed that neoplasia onset and mortality are independently associated with low baseline plasma TC and LDL levels at admission for ACS.

Abbreviations

ACS: Acute coronary syndrome; AMI: Acute myocardial infarction; CAD: Coronary artery disease; CI: Confidence intervals; CK: Creatine kinase; CK-MB: Creatine kinase MB; CVD: Cardiovascular disease; HDL: High-density lipoprotein; HR: Hazard ratios; LDH: Lactate dehydrogenase; LDL: Low-density lipoprotein; MFF: Modified Friedewald formula; NSTEMI: Non-ST elevation myocardial infarction; STEMI: ST-elevation myocardial infarction; TC: Total cholesterol; TG: Triglycerides

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Availability of data and materials

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

Authors' contributions

GB and FC designed the study. RC and FB contributed to the original data collection. FC and RC contributed to data handling and patient follow-up. GB and HTM contributed to the data analysis, interpretation and manuscript preparation. HTM and MP contributed to the tables and figures preparation. All authors contributed to ensuring the accuracy of the data analysis. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study has been performed in accordance with the Declaration of Helsinki and it was approved by Adria, Bassano del Grappa and Conegliano General hospitals ethics committee.
All enrolled patients gave their written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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