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Routine laboratory tests to risk-stratify patients with chronic coronary artery disease

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ABSTRACT

Background: Several biohumoral variables, taken individually, are predictors of prognosis in patients with chronic coronary artery disease (CAD). We hypothesized that taken together, laboratory tests provide prognostic information that is additive to a complete diagnostic work-up.
Methods: We prospectively examined 2370 consecutive patients with chronic CAD, as shown by a >50% coronary stenosis (in 95% of patients), previous coronary revascularization (in 31% of patients), and/or previous myocardial infarction (MI, in 54% of patients). We tested the ability of laboratory and clinical variables to predict future cardiac events (cardiac death and non-fatal MI).
Results: During follow-up (median, 46 months), 147 patients (6.2%) died from cardiac causes and 81 (3.4%) experienced a non-fatal MI. Using multivariate analysis, after adjustment for clinical variables (including left ventricular ejection fraction and angiographic extent of coronary stenoses), a high-density lipoprotein cholesterol (HDLc) concentration < 35 mg/dL ($p < 0.0001$), a neutrophil-to-lymphocyte ratio >2.4 ($p = 0.0014$), and an fT3 serum level < 2.1 pg/mL with normal thyrotropin (low-T3 syndrome) ($p = 0.0260$) showed an independent and incremental prognostic value, and were associated with an increase in the rate of cardiac events of 86%, 57% and 41%, respectively. When these variables were added to clinical and instrumental variables, the prognostic power of the model increased significantly (global chi-square improvement: from 157.01 to 185.07, $p < 0.0001$).
Conclusion: Low HDLc, high neutrophil-to-lymphocyte ratio and low-T3 syndrome, both individually and taken together, provide prognostic information that is independent of and incremental to the main clinical and instrumental findings.

Introduction

In the management of patients with chronic CAD, laboratory tests are performed very frequently in order to identify biohumoral cardiovascular risk factors, to monitor their trends, to assess the effectiveness and safety of therapy, and preliminary to invasive investigations and contrast media administration [1]. Various studies have examined the effect of individual biohumoral variables on the prognosis of patients with chronic CAD. We tested the hypothesis that laboratory tests, taken together, provide additional prognostic information in patients with chronic CAD, and that this information is independent of and incremental to commonly analyzed clinical and instrumental variables.

Methods

Patients

Of 8522 patients admitted to the Cardiology Unit of our Institute between 2001 and 2007, we prospectively studied a group of consecutive patients at their first hospital admission for chronic CAD. Inclusion criteria were: (a) history of stable angina or the evidence of inducible myocardial ischemia associated with coronary stenoses that reduced the lumen of one or more coronary arteries by >50%, (b) previous coronary artery bypass graft surgery, (c) previous percutaneous coronary intervention, and/or (d) the documentation of a previous myocardial infarction (MI) by clinical records. Out of 2871 patients initially screened, we excluded 373 patients for a clinical course compatible with an acute MI, 36 patients in whom the final diagnosis was cardiomyopathy or myocarditis, 33 patients for associated valvular heart disease of at least moderate entity, 10 patients for chronic renal failure under hemodialysis treatment and

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Table 1
Clinical characteristics of patients.

Patient characteristics	Overall $n = 2370$	With events $n = 228$	Without events $n = 2142$	p-Value
Age, mean (SD), years	67 (10)	70 (9)	67 (10)	**<0.0001**
Male, *n* (%)	1865 (79)	183 (80)	1682 (79)	0.542
Family history of premature CAD, *n* (%)	1144 (48)	103 (45)	1041 (49)	0.325
Diabetes mellitus, *n* (%)	628 (26)	86 (38)	542 (25)	**<0.0001**
Hypertension, *n* (%)	1435 (60)	138 (61)	1297 (61)	0.994
Hypercholesterolemia, *n* (%)	1663 (70)	140 (61)	1523 (71)	0.0023
Obesity, *n* (%)	663 (28)	55 (24)	608 (28)	0.172
Smoker in the last year, *n* (%)	1165 (49)	104 (46)	1061 (50)	0.260
Previous myocardial infarction, *n* (%)	1269 (54)	147 (64)	1122 (52)	**0.0005**
Exertional angina, *n* (%)	627 (26)	45 (20)	582 (27)	**0.0176**
Angina at rest, *n* (%)	438 (19)	41 (18)	397 (19)	0.8584
Mixed angina, *n* (%)	689 (29)	71 (31)	618 (29)	0.4901
Previous coronary artery bypass surgery, *n* (%)	284 (12)	52 (23)	232 (11)	**<0.0001**
Previous percutaneous coronary interventions, *n* (%)	456 (19)	47 (21)	409 (19)	0.580
Left ventricular ejection fraction, mean (SD), %	52 (11)	44 (14)	52 (11)	**<0.0001**
Disease of one coronary vessel, *n* (%)	841 (36)	48 (21)	793 (37)	**<0.0001**
Disease of two coronary vessels, *n* (%)	602 (25)	72 (32)	530 (25)	**0.0253**
Disease of three coronary vessels, *n* (%)	404 (17)	58 (25)	346 (16)	**0.0005**
Disease of the left main stem, *n* (%)	234 (10)	36 (16)	198 (9)	**0.0025**
Disease of secondary vessels only, *n* (%)	175 (7)	9 (4)	166 (8)	**0.0443**
Non-significant stenosis, *n* (%)	114 (5)	5 (2)	109 (5)	0.0706

CAD, coronary artery disease.
Bold values have been utilized to indicate statistically significant variables.

9 patients for overt hyperthyroidism. During hospitalization, each patient had undergone a diagnostic work-up that included laboratory testing, two-dimensional echocardiography, and coronary angiography. The characteristics of the 2370 patients studied are illustrated in Table 1.

The criteria used to define diabetes mellitus, arterial hypertension, hypercholesterolemia and obesity were consistent with international guidelines [2–4]. The left ventricular (LV) ejection fraction was measured by two-dimensional echocardiography using the single-plane or the biplane Simpson's rule. After reading the coronary arteriography, each patient was assigned an angiographic score whereby 1 = single vessel disease, 2 = two-vessel disease, 3 = three-vessel disease, 4 = disease of left main stem, 0.5 disease of secondary vessels only, and 0 = absence of significant coronary stenoses [5]. The LV ejection fraction was <35% in 13% of patients, and ranged between 35 and 50% in 24% of patients. A multi-vessel coronary artery disease or a stenosis of the left main stem were present in 52% of patients.

Laboratory tests

The first day of hospital admission, samples of peripheral venous blood were drawn from the antecubital vein after patient overnight fasting, and processed for a complete series of routine laboratory assays. The laboratory variables explored were hematocrit, white blood cell (WBC) count, neutrophil-to-lymphocyte (N/L) ratio, platelet count, fasting glucose, serum creatinine, total cholesterol, high-density lipoprotein cholesterol (HDLc), triglycerides, TSH, fT3, fT4, and C-reactive protein. Low-density lipoprotein cholesterol (LDLc) concentration was calculated using the Friedewald equation [6]. The glomerular filtration rate (eGFR) was estimated according to the Cockcroft–Gault formula [7]. All laboratory tests were analyzed as categorical variables based on the normal values of our laboratory or previous studies. Although in current guidelines the cut-off value for low HDLc is 40 mg/dL [8], we considered a cut-off value of 35 mg/dL [9] because HDLc concentrations below this threshold were more strictly associated with cardiac events in our patient population. The cut-off value of serum creatinine was set to 1.4 mg/dL [10,11]. The cut-off value of eGFR was set to 30 mL/min. Low T3 syndrome was defined as fT3 serum level < 2.1 pg/mL without accompanying TSH increase, hypothyroidism was defined as TSH > 3.8 μIU/mL [12]. An N/L ratio of 2.42 was chosen on the basis of previous studies from the same institution [13].

Follow-up

The entire group of patients was followed for up to 7 years (median, 46 months). Patients were followed-up by periodic examinations in the outpatient setting. In patients who did not attend this program, follow-up data were obtained using a written telephone interview (administered to the patient or the patient's family by dedicated personnel) or mail questionnaires. In case of negative answers, the local demographic registry was queried. Cardiac death was defined as death caused by acute MI, death caused by heart failure, or sudden and unexpected death not related to any possible cause. The diagnosis of non-fatal MI was documented by clinical records. The study protocol was approved by the local committee on human research. In addition, patients gave written informed consent to have their clinical data prospectively collected for research purposes.

Statistical analysis

Continuous variables were expressed as mean and SD, categorical variables as percentages. The primary endpoint was the occurrence of cardiac events, defined as cardiac death or non-fatal MI. Predictors of survival were identified using univariate and multivariate analysis, performed using the Cox proportional hazards regression model. Categorical variables were included in the model as dummy variables. Only those variables resulting significant at univariate analysis were entered into the regression model; the significant variables at multivariate analysis were selected using a backward elimination procedure. Analysis was initially limited to the clinical and instrumental variables. Thereafter, laboratory variables were examined, both before and after adjustment for the independent clinical and instrumental predictors of survival, as well as for medical treatment and myocardial revascularization. The incremental prognostic information obtained after including laboratory variables was evaluated by the chi-square. All statistical tests were two-tailed; a p-value < 0.05 was considered significant. Statistical analysis was performed with the software program JMP 9 [SAS Institute Inc.] and R: A Programming Environment for Data

Table 2
Laboratory variables.

Variable	Overall $n=2370$	With events $n=228$	Without events $n=2142$	p-Value
Htc, mean (SD), (%)	41.1 (4.7)	40.2 (5.3)	41.2 (4.6)	**0.0036**
WBC/mm^3, mean (SD)	7.5 (2.2)	7.7 (2.2)	7.4 (2.2)	0.0993
Neutrophil/lymphocyte ratio, mean (SD)	2.6 (2.2)	3.3 (3.0)	2.6 (2.1)	**<0.0001**
PLT/mm^3, mean (SD)	226.6 (67.2)	224.4 (69.4)	226.8 (67.0)	0.6059
Glucose, mean (SD), (mg/dL)	107.7 (36.6)	111.4 (38.0)	107.4 (36.4)	0.1171
Creatinine, mean (SD), (mg/dL)	1.1 (0.3)	1.2 (0.4)	1.0 (0.3)	**<0.0001**
Total cholesterol, mean (SD), (mg/dL)	184.8 (42.9)	180.2 (43.0)	185.2 (42.8)	0.0948
HDL cholesterol, mean (SD), (mg/dL)	40.4 (11.1)	39.8 (12.9)	40.4 (10.9)	0.3790
LDL cholesterol, mean (SD), (mg/dL)	119.2 (36.9)	116.3 (34.6)	119.5 (37.1)	0.2130
Triglycerides, mean (SD), (mg/dL)	129.7 (77.4)	124.5 (59.3)	130.2 (79.0)	0.3185
Low T3 syndrome, n (%)	585 (26)	79 (34.6)	506 (23.6)	**0.0003**
Hypothyroidism, n (%)	205 (9)	179 (78.5)	26 (1.2)	**<0.0001**
C-reactive protein, mean (SD), (mg/dL)	1.0 (2.8)	1.1 (2.8)	0.9 (2.8)	0.4718

Htc, hematocrit; WBC, white blood cells; PLT, platelet count; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Bold values have been utilized to indicate statistically significant variables.

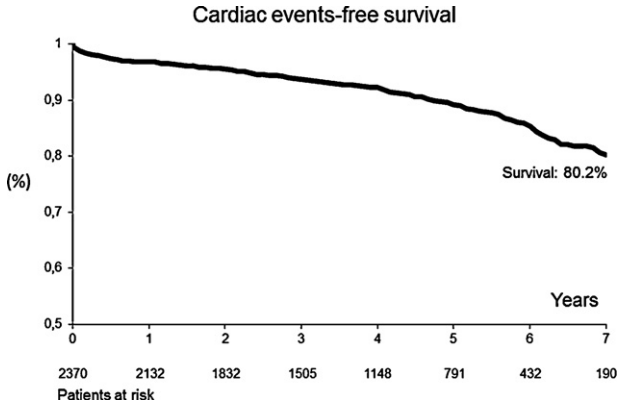

Fig. 1. Cardiac event-free survival in the entire population.

Analysis and Graphics, version 2.7.1 [R Foundation for Statistical Computing].

Results

During follow-up (median, 46 months), 277 of the 2370 patients died, 147 of whom from cardiac causes, and 81 experienced a non-fatal MI. The 7-year rate of cardiac events (cardiac death and non-fatal MI) was 19.8%. A plot of cardiac event-free survival in the whole population is shown in Fig. 1. Patients with cardiac events were older, more frequently diabetic, and more frequently had a previous MI or previous coronary artery bypass graft surgery than patients without events. Furthermore, patients with events had lower LV ejection fraction and more severe coronary atherosclerosis than those without events during follow-up (Table 1). At Multivariate Cox regression analysis, the following clinical and instrumental variables were significant independent predictors of event-free survival: age (HR 1.04, 95% confidence interval [CI]: 1.02–1.05, $p<0.0001$), diabetes mellitus (HR 1.39, 95%CI: 1.06–1.82, p 0.0194), LV ejection fraction (HR 0.96, 95%CI: 0.95–0.97, $p<0.0001$) and the extent of coronary stenoses (HR 1.33, 95%CI: 1.19–1.50, $p<0.0001$). A 1-year increase in age, the presence of diabetes, a 1% increase in ejection fraction, and a 1-point increase in coronary angiographic score were associated with a change in the risk of cardiac events by 4%, 39%, −4% and 33%, respectively.

As shown in Table 2, patients with cardiac events during follow-up had higher N/L ratio, higher creatinine levels, and presented hypothyroidism or low T3 syndrome more frequently than did those without events. Table 3 shows the laboratory predictors of event-free survival at univariate analysis. After adjustment for the clinical and instrumental variables, the significant laboratory predictors of survival were low hematocrit, elevated N/L ratio, elevated serum creatinine, low HDLc concentration and low T3 syndrome (if considered separately). Using multivariate analysis, and after adjustment for the clinical and instrumental variables, the laboratory independent predictors of a worse survival were HDLc concentration < 35 mg/dL, N/L ratio > 2.42 and a low T3 syndrome (Table 4, upper panel). A low HDLc, an elevated N/L ratio and a low T3 syndrome were associated with an increase in the rate of cardiac events of 86%, 57% and 41%, respectively. Plots of cardiac

Table 3
Laboratory predictors of cardiac event-free survival using univariate analysis, both before and after adjustment for the clinical and instrumental variables.

Variable	Not adjusted			Adjusted for clinical and instrumental variables		
	HR	95% CI	p-Value	HR	95% CI	p-Value
Htc < 36% if male, <40% if female	1.71	1.31–2.24	**0.0003**	1.33	1.01–1.75	**0.0409**
WBC > 11.900 mm^{-3}	1.45	0.75–2.54	0.2487	1.42	0.73–2.49	0.2823
Neutrophils/lymphocytes > 2.4	1.76	1.36–2.30	**<0.0001**	1.68	1.29–2.19	**0.0001**
PLT > 410 mm^{-3}	1.20	0.43–2.62	0.6928	1.25	0.44–2.72	0.6399
Glucose > 110 mg/dL	1.42	1.09–1.86	**0.0101**	1.05	0.78–1.42	0.7171
Creatinine > 1.4 mg/dL	2.88	2.11–3.88	**<0.0001**	1.69	1.21–2.31	**0.0022**
Total cholesterol > 200 mg/dL	0.89	0.67–1.18	0.4366	1.06	0.79–1.40	0.6632
HDL cholesterol < 35 mg/dL	1.87	1.43–2.44	**<0.0001**	1.95	1.48–2.57	**<0.0001**
LDL cholesterol > 100 mg/dL	0.94	0.71–1.25	0.6635	1.03	0.78–1.37	0.8421
Triglycerides > 150 mg/dL	1.06	0.79–1.41	0.6816	1.20	0.88–1.61	0.2394
Low T3 syndrome	1.74	1.30–2.33	**0.0002**	1.56	1.16–2.09	**0.0032**
Hypothyroidism	1.83	1.17–2.76	**0.0093**	1.46	0.92–2.21	0.0988
C-reactive protein > 0.4 mg/dL	1.38	1.05–1.81	**0.0197**	1.27	0.97–1.68	0.0791

HR, hazard ratio; CI, confidence interval; Htc, hematocrit; WBC, white blood cells; PLT, platelet count; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Bold values have been utilized to indicate statistically significant variables.

Table 4
Final independent laboratory predictors of cardiac event-free survival using multivariate analysis, after adjustment for the clinical and instrumental variables.

Variable	Adjusted for clinical and instrumental variables		
	HR	95% CI	*p*-Value
HDL cholesterol < 35 mg/dL	1.86	1.40–2.46	<0.0001
Neutrophils/lymphocytes > 2.4	1.57	1.19–2.08	0.0014
Low T3 syndrome	1.41	1.04–1.91	0.0260
HDL cholesterol < 35 mg/dL	1.80	1.34–2.40	<0.0001
Neutrophils/lymphocytes > 2.4	1.52	1.14–2.02	0.0039
Low T3 syndrome	1.35	0.99–1.85	0.0570
eGFR < 30 mL/min	3.12	1.73–5.36	0.0003

HR, hazard ratio; CI, confidence interval; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate.

event-free survival for patients with HDLc≥ or <35 mg/dL, with N/L ratio≤ or >2.42, or with or without low T3 syndrome are illustrated in Fig. 2. When renal function was estimated by the eGFR, a value of <30 mL/min became an independent predictor of cardiac event-free survival (Table 4, lower panel). Of note, low T3 syndrome lost part of its statistical significance.

Adding to the clinical and instrumental variables those extracted from laboratory tests, the prognostic information increased significantly. As a matter of fact, the global chi-square improved from 157.01 (clinical and instrumental variables) to 185.07 (+laboratory variables; $p < 0.0001$). Considering cardiac death as the only end-point, low HDLc, high N/L ratio and low T3 syndrome remained independent predictors of survival. Considering non-fatal MI as the only end-point, low HDLc concentration was the only laboratory predictor of event-free survival. In a subgroup analysis, low T3 syndrome was not an independent predictor of event-free survival in females, in patients younger than age 65 years, and in those with LV ejection fraction ≥40%.

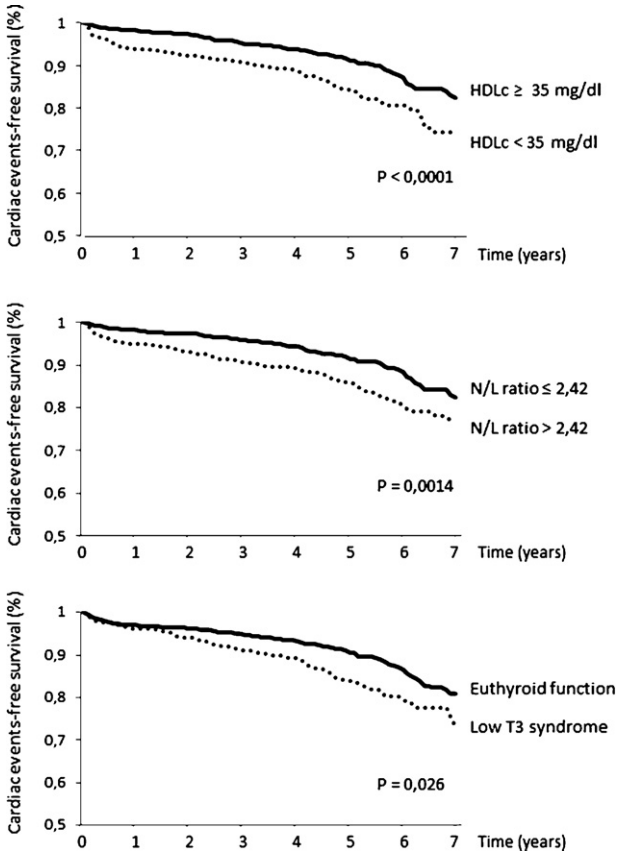

Fig. 2. Plots of cardiac event-free survival for patients with HDLc≥ or <35 mg/dL (top panel), N/L ratio≤ or >2.42 (middle panel), or with or without low T3 syndrome (lower panel).

Patients with and without cardiac events did not significantly differ as to beta-blockers, calcium antagonists, ACE inhibitors or nitrate treatment, while they differed as to antiplatelet agents, anticoagulant and lipid-lowering agents (Table 5). Patients with and without events did not differ as to myocardial revascularization by coronary artery bypass graft surgery or percutaneous coronary interventions (Table 5). In order to explore whether differences in medical treatment could have affected the ability of laboratory variables to predict patient outcome, the regression model was repeated after adjustment for the antiplatelet and anticoagulants agents, lipid-lowering agent and coronary revascularization procedures. Low HDLc ($p = 0.0004$), high N/L ratio (0.0087) and eGFR < 30 mL/min remained independent predictors of event-free survival, while low T3 syndrome lost its predictive power ($p = 0.1729$).

Discussion

This study shows that routine laboratory tests, both individually and taken together, provide independent and incremental information on the prognosis of patients with chronic CAD. It is known that alterations in lipid metabolism, renal function, thyroid homeostasis and complete blood count – taken individually – can influence the prognosis of CAD patients. This study shows that this information is independent and additive with respect to clinical variables. The ability to predict cardiovascular events is in fact maintained even after adjusting for the main factors that emerge from a comprehensive diagnostic work-up, and after adjustment for medical treatment and coronary revascularization.

Low HDL cholesterol

For many years our efforts in the prevention and treatment of CAD have been primarily aimed at lowering LDLc [14]. However, it has been known since the Framingham Study that cardiovascular risk is also influenced by HDLc [15], which facilitates reverse cholesterol transport and exerts an antioxidant activity [16]. Thus, an estimated 1 mg/dL higher HDLc is associated with a 2% lower risk of CAD for men and a 3% lower risk for women, while low levels of HDLc are associated with a more unfavorable cardiovascular prognosis [17]. In our patients with chronic CAD, LDLc did not appear to exert any effect on the prognosis while low HDLc levels had a negative prognostic impact. In the author's opinion, the effects of LDLc on survival are blunted in this study by the pharmacological treatment – mainly statins – which reduces LDLc but has little effect on HDLc.

How low HDLc must be in order to negatively affect patients' outcome deserves some consideration. In our population HDLc concentrations < 40 mg/dL were found in 41% of patients, and were not associated with prognosis after adjustment for clinical variables ($p = 0.86$). However, HDLc concentrations < 35 mg/dL, which occurred in 32% of patients, affected the prognosis adversely, even after adjustment for clinical variables ($p < 0.0001$). Therefore, it is the very low levels of HDLc that must be regarded with particular attention in order to risk-stratify CAD patients [18].

Finally, the results of this study underline, if needed, the prognostic impact of lipid-lowering drugs, which proved to be an independent predictor of event-free survival.

Low T3 syndrome

The effects of abnormal thyroid metabolism on the cardiovascular system have been known for many years [19]. Specifically, low T3 syndrome, characterized by reduced serum levels of total and

Table 5
Medical treatment and myocardial revascularization.

Variable	Overall$n = 2370$	With events$n = 228$	Without events$n = 2142$	p-Value
Antiplatelet, *n* (%)	1976 (83)	170 (74)	1806 (84)	**0.0002**
Anticoagulants, *n* (%)	559 (24)	79 (34)	480 (22)	**<0.0001**
Beta blockers, *n* (%)	1449 (61)	129 (56)	1320 (61)	0.1373
Calcium antagonists, *n* (%)	332 (14)	35 (15)	297 (13)	0.5437
Angiotensin-converting enzyme inhibitors, *n* (%)	1042 (43)	99 (43)	943 (44)	0.8615
Nitrates, *n* (%)	1608 (67)	149 (65)	1459 (68)	0.3958
Lipid-lowering agents, *n* (%)	1762 (74)	144 (63)	1618 (75)	**<0.0001**
Coronary artery bypass graft surgery, *n* (%)	517 (21)	52 (22)	465 (21)	0.7026
Percutaneous coronary interventions, *n* (%)	1166 (49)	114 (50)	1052 (49)	0.7990

Bold values have been utilized to indicate statistically significant variables.

free T3 in the presence of serum TSH and fT4 within normal limits, has proved to be a powerful determinant of prognosis in patients with chronic heart failure [12]. Increased mortality in low T3 syndrome has also been observed in patients with acute MI [20]. More recently, an inverse correlation between fT3 levels and coronary atherosclerosis has been found in a series of patients with CAD in the absence of previous MI and LV dysfunction [21]. In this study more than half of the patients had a previous MI, and over one-third had an LV ejection fraction of <50%. This study further confirms the negative prognostic impact of low T3 syndrome in an unselected group of patients with chronic CAD. In addition, a subgroup analysis has shown that the negative prognostic impact of low T3 syndrome is mainly present in male patients, in patients older than 65 years, and in those with LV ejection fraction < 40%. Very recently, low T3 was associated with exercise capacity, but only in patients with severe functional impairment [22].

CBC with differential

Previous studies have shown leukocytosis to be an independent predictor of future cardiovascular events, both in healthy individuals and in patients with stable angina, unstable angina, or a history of myocardial infarction [23]. In our population WBC count did not show any predictive power, confirming previous investigations [24]. Complete blood count differential deserves a different consideration. Very recently, the usefulness of the N/L ratio (an emerging marker of inflammation) in predicting short- and long-term mortality has been shown in patients with non-ST-elevation myocardial infarction and in those with decompensated heart failure [25,26]. Our study extends to a larger patient population previous observations on the association between the N/L ratio and patient outcome in chronic CAD [13]. Accordingly, relative lymphocyte count should be incorporated into clinical decisionmaking models to facilitate risk stratification in CAD.

After adjustment for potential confounders, a low baseline hematocrit has been shown to be a predictor of early and late mortality in patients undergoing percutaneous coronary interventions [27], coronary artery bypass graft surgery [28], and in those with acute MI [29]. Finally, anemia proved to be an independent predictor of death and major adverse events among elderly patients with stable CAD [30], as confirmed in our patient population. The fact that anemia was not an independent predictor of survival at multivariate analysis likely reflects the interference with other factors, such as kidney disease.

Serum creatinine and eGFR

Cardiovascular mortality is 10–30 times higher in dialysis patients than in the general population [31,32]. To avoid the well-known prognostic effects of chronic kidney disease, we excluded patients who were on hemodialysis. However, even small increases in serum creatinine are associated with a worse cardiovascular prognosis [33], as confirmed in our cohort of patients. On a practical level, patients with even mild forms of renal failure must be considered high cardiovascular risk patients, for whom we must aim to achieve more ambitious therapeutic goals. Of note, serum creatinine was not an independent predictor of survival at multiple logistic regression, while the eGFR was. This observation further underlines the advantages of estimating the glomerular filtration rate over a simple measurement of creatinine concentration in the clinical setting.

C-reactive protein

In patients with acute coronary syndrome, plaque rupture causes an increase in systemic indicators of inflammation, such as C-reactive protein. In this setting, high levels of C-reactive protein are predictors of a worse prognosis. However, C-reactive protein is a relatively moderate predictor of coronary heart disease [34], also because its value can be affected by concomitant therapies such as acetyl salicylic acid, by exposure to cigarette smoke or by concomitant renal insufficiency. Our data on patients with chronic CAD are consistent with these data, since C-reactive protein lost its predictive value after adjustment for clinical and laboratory variables.

Study limitations

Thanks to the interdisciplinary nature of our research institute, and in view of coronary angiography, we performed assays of thyroid hormones and TSH in every patient. These laboratory examinations are not performed routinely in every center. Furthermore, we did not analyze in every patient the levels of neurohormones [35], which have been shown to be related with patient outcome, nor the levels of new biomarkers [36]. In addition, laboratory tests were performed at initial patient admission, and we have no data regarding the changes in laboratory variables over time, nor patients' adherence to medical treatment. Finally, the use of medications in our patients does not perfectly match current guidelines, but is similar to that of the REACH registry [37], which reflects the current standard of care. Since the COURAGE trial was published in 2007 [38], more intensive medical therapy has been conducted.

Conclusion

Routine laboratory tests are widely available, cheap, and easy to interpret. In patients with chronic CAD, several of these tests provide independent and incremental prognostic information that cannot be replaced by even accurate clinical and instrumental examination. The results of this study are in line with a holistic view of the patient, since the prognosis of CAD patients is only partly predicted by the extent of coronary lesions and by LV dysfunction, while the outcome is largely influenced by non-cardiac variables such as age, diabetes mellitus, blood cell count, lipid metabolism, thyroid metabolism and kidney function.

Conflict of interest

None.

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