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Orginal Contribution

A new simple risk score in patients with acute chest pain without existing known coronary disease

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Abstract

Objective: To derive and validate a prediction rule in patients with acute chest pain (CP) without existing known coronary disease.

Methods: Cohort study including 2233 patients with CP. Based on clinical judgment, 1435 were discharged as very low risk and the remaining 798 underwent exercise tolerance test (ETT). End point: 6-month composite of cardiovascular death, nonfatal myocardial infarction, and revascularization. The prediction rule was derived from a randomly selected test cohort (n = 1106) summing factors of variables selected by multivariate regression analysis: CP score higher than 6 (factor of 3), male gender, age older than 50 years, metabolic syndrome, and diabetes mellitus (factor of 1, for each). The prediction rule was validated in the remaining cohort (n = 1127). All patients with CP were categorized into 3 groups: group A (prediction rule 0-1), B (2-4), or C (5-6). Outcomes and prognostic yield of ETT were compared among each group.

Results: In the test cohort, 55 patients (5%) reached the composite end point. Event rate increased as the prediction rule increased: 1% for group A, 6% for B, and 25% for C ($P < .001$). This pattern was confirmed in the validation cohort ($P < .001$). A normal ETT did not significantly improve the high (99%) negative predictive value in group A and did not succeed in excluding the composite end point (17%) in group C.

Conclusions: In patients with acute CP without existing coronary disease, a prediction rule based on clinical characteristics provided a useful method for prognostication with possible implication in decision making.

1. Introduction

Patients with chest pain (CP) and nondiagnostic initial work-up, including electrocardiogram (ECGs) and serial troponins, and without existing known coronary artery

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disease are currently considered at low risk of short-term coronary events (<2% of death and/or myocardial infarction) [1,2]. However, in that large and heterogeneous population with a mean low prevalence of coronary disease, diagnosis of acute coronary syndrome still represents a challenge. In low-risk patients, a stress test aids the evaluation of suspected coronary disease and it is usually performed in the Emergency Department (ED), in the CP unit, or on an outpatient basis shortly after discharge; however, submitting patients to this diagnostic strategy is usually based on unstandardized clinical judgment [2-4]. In patients with defined acute coronary syndrome, several prediction rules are available for risk stratification [5-7]; conversely, no study has validated the usefulness of a prediction rule including coronary risk factors [8-11] in a large cohort of patients with low-risk CP. Moreover, some of the major risk factors for atherosclerosis (eg, hypertension, hypercholesterolemia, obesity, cigarette smoking, family history) have been found to be weakly predictive of the likelihood of coronary events in this population [12,13]. Recently, a cluster of coronary risk factors defined as metabolic syndrome (MS) have received attention in global cardiovascular risk assessment, similar to the awareness diabetes mellitus (DM) has received [14-16]. To our knowledge, the usefulness of including MS in the diagnostic work-up of patients with acute CP has not been evaluated. Indeed, no standardized prediction rule is yet available for stratification of patients with low-risk CP in the ED [2,17]. Thus, the primary goal of this study was to derive and validate in an ED a clinical prediction rule for prognostication in patients with low-risk CP.

2. Methods

2.1. Patient selection

Consecutive adult patients with CP who presented to our ED (tertiary care teaching hospital), during the years 2002 to 2005, with normal ECG and normal troponin levels were admitted to the CP unit and considered for the study [2]. Patients with existing known coronary artery disease or with a life expectancy less than 6 months were excluded from the study. All patients gave their written consent for study participation. The study was approved by the local institutional review board.

2.2. Management of patients and study protocol

In the CP unit, all patients underwent a first-line, 6-hour work-up with characterization of CP by a previously validated CP score (Table 1) [18], serial 12-lead ECGs [2,19], and serial troponins. Moreover, the presence of DM, MS, arterial hypertension, familial history of coronary disease (≤65 years old), and current smoking was evaluated.

Table 1 Chest pain score

Location	
Substernal, precordial	+3
Left chest, neck, lower jaw, epigastrium	+1
Radiation	
Either arm, shoulder, back, neck, lower jaw	+1
Character	
Crushing, pressing, heaviness	+3
Sticking, pleuritic, pinprick	+1
Associated symptoms	
Dyspnea, nausea, diaphoresis	+2
Previous history of CP	+3

Diagnosis of MS consisted of history or presence of 3 or more of the following: high fasting glucose (>110 mg/dL), high blood pressure (systolic blood pressure >130 mm Hg and diastolic blood 80 pressure >85 mm Hg), low high-density lipoprotein cholesterol (<40 mg/dL in men and <50 mg/dL in women), high triglycerides (>150 mg/dL), and central obesity (waist circumference >102 mm in men and 88 mm in 82 women) [14,15]. Diagnosis of DM consisted of history or presence of fasting glucose greater than 125 mg/dL in at least 2 measurements. Patients with DM were excluded from the MS group. Baseline clinical characteristics of patients of the study were derived from anamnestic data obtained from patients, parents, caregivers, or events analyzed by review of previous hospital or laboratory data that are available on the hospital network. When we were not able to obtain any information regarding some of the considered risk factors, we concluded that the patient did not have that risk factor, avoiding overestimation of coronary risk profile. Resting echocardiography was performed in all patients [2,17].

During the management in the CP unit, patients who were found as having ischemic ECG changes [18], and/or abnormal troponin I levels, and/or wall motion abnormalities at echocardiography were considered at high risk of coronary events; thus they were referred for urgent coronary angiography [19,20]. Patients with normal serial ECG and troponins, normal echocardiography, and a CP score lower than 4 were considered at very low risk of coronary disease [2,17] and they were discharged and followed up at 6 months. The remaining patients with CP score higher than 4 and without existing known coronary disease were considered low-risk patients and underwent early in-hospital maximal exercise tolerance test (ETT) [4,18]. Patients with a positive test were considered at high risk of coronary events; they were admitted and referred for early coronary angiography [19-21]. Conversely, patients with normal ETT were considered at very low risk; they were discharged home and followed up at 6 months [17,22]. Follow-up data were gathered by means of monthly telephonic interviews up to the sixth month, and all events were analyzed by review of hospital and laboratory data.

2.3. End point

The primary outcome was a composite of cardiovascular death, nonfatal myocardial infarction, or new or recurrent severe cardiac ischemia requiring urgent revascularization. Acute myocardial infarction was defined according to international guidelines [23].

2.4. Statistical analysis

A multivariate model for prognostication of risk for experiencing at least 1 element of the composite end point was developed. The model incorporated baseline characteristics previously reported to be important [24-28]. The model derivation was restricted to the test cohort of patients selected by retrospective random sampling of about 50% of the overall population (n = 1106). A total of 7 baseline characteristics arranged in a dichotomous fashion were screened as candidate predictors (Table 2). After each variable was tested in a univariate regression model, those that achieved a significance level of $P < .20$ were selected for testing in a multivariate stepwise (backward elimination) logistic regression model. Variables associated with $P < .05$ were retained in the final model. By the developed multivariate model 5 variables were included. A factor directly proportional to the odds ratio of that variable was assigned: a factor of 3 for CP score higher than 6; a factor of 1 for each of male sex, age older than 50 years, MS, and DM. The rule was then calculated by arithmetic sum and was validated in the validation cohort. We tested for homogeneity the prediction rule in the validation cohort by comparing the slope of the increase of event rate with the increase in the score of the Florence prediction rule using least squares linear regression analysis. To asses the model's discrimination power to predict the composite end point, we compared the area under the receiver operating characteristic curve between the validation and the test cohort [29,30]. Fisher exact test was used when expected frequencies are less than 5. *P* values are 2 sided, and a *P* value of less than .05 was considered to indicate statistical significance. Calculations were performed with the SPSS statistical package (version 14, SPSS, Inc, Chicago, Ill).

3. Results

During the years 2002 to 2005, 6396 patients with CP were evaluated (Fig. 1). Of these, 3751 were considered at high risk of short-term coronary events and were excluded from the study [19,20]. The remaining 2645 patients, with normal ECG, were admitted to our CP unit [2,17]. During the first-line work-up, 389 patients developed ischemic ECG changes, and/or abnormal troponins, and/or wall motion abnormalities at echocardiography; all these patients were considered at high risk of coronary events and were referred for urgent coronary angiography [19,20]. The work-up was normal in 2256 patients; 23 patients declined to participate in the study; therefore 2233 patients were included in the study. Of these, 1435 were considered at very low risk and were discharged from the CP unit, whereas 798 were considered at low risk and underwent in-hospital ETT. Those with positive ETT (n = 142, 17.8%) were admitted, whereas those with normal ETT (n = 656, 82.2%) were discharged as very low risk patients (Fig. 1).

The clinical characteristics of patients enrolled are shown in Table 2. At 6-month follow-up, no patient was lost to follow-up and no patient died; 108 patients (4.8%)

Table 2 Baseline characteristics of patients with CP and nondiagnostic initial work-up

	Total (N = 2233)	Test cohort (n = 1106)	Validation cohort (n = 1127)	*P*
Age (y)	50.5 ± 14.9	50.31 ± 14.8	50.8 ± 15	.467
Gender (male)	1358 (59.9%)	670 (60.6%)	688 (61%)	.828
Diabetes	131 (5.9%)	58 (5.2%)	73 (6.5)	.242
Metabolic syndrome	114 (5.1%)	57 (5.2%)	57 (5.1%)	.924
Hypertension	380 (17%)	187 (16.9%)	193 (17.1%)	.910
Hyperlipemia	303 (13.6%)	159 (14.4%)	144 (12.8%)	.293
Central obesity	65 (2.9%)	31 (2.8%)	34 (3.0%)	.802
Fasting glucose	131 (8.6%)	89 (8%)	102 (9.1%)	.406
Smokers	246 (11%)	116 (10.5%)	130 (11.5%)	.457
Familiarity for CAD	88 (3.9%)	43 (3.9%)	45 (4.0%)	.914
Chest pain score	3.3 ± 2.6	3.3 ± 2.6	3.3 ± 2.6	.844
Primary outcome	108 (4.8%)	55 (5%)	53 (4.7%)	.768
Urgent revascularization	81 (3.6%)	44 (4%)	37 (3.3%)	.429
Myocardial infarction	32 (1.4%)	14 (1.3%)	18 (1.3%)	.594
Death	0	0	0	1.000

CAD indicates coronary artery disease.

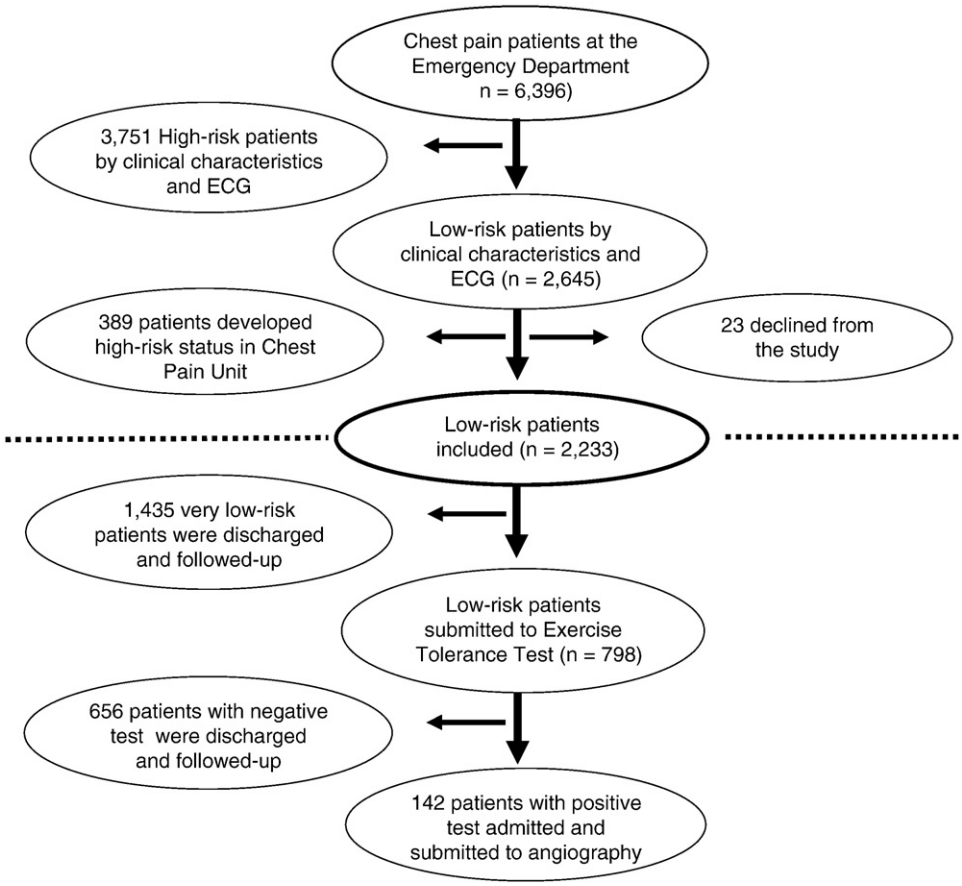

Fig. 1 Flow diagram of participants in the study.

reached the composite end point of myocardial infarction or revascularization.

3.1. Derivation of the Florence prediction rule

The test cohort for development of the Florence prediction rule consisted of a randomized sample of 1106 patients; in this cohort, 5.0% reached the end point (Table 2). Of 7 original candidate variables, only 5 proved to be significant in the multivariate analysis and formed the final group of predictor variables (Table 3). As the parameter estimate of CP score higher than 6 had a magnitude about 3-fold higher than the others, the risk score was calculated giving a value of 3 to CP score higher than 6 and a value of 1 to all the other variables when present (Table 3). Thus, patients in the test cohort were categorized by the sum of assigned values, obtaining 7 categories as shown in Fig. 2. There is a progressive, significant pattern of increasing event

Table 3 Association between clinical variables and composite end point (death and/or acute myocardial infarction and/or urgent coronary revascularization) at univariate and multivariate logistic regression analysis

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
Chest pain score >6	11.21	6.33-19.84	<.001	7.03	3.80-12.99	<.001
Metabolic syndrome	6.23	3.08-12.64	<.001	3.03	1.36-6.79	.007
Age >50 y	5.11	2.55-10.25	<.001	2.87	1.38-6.07	.005
Diabetes mellitus	3.41	1.53-7.60	.003	2.56	1.07-6.16	.035
Gender (male)	1.78	0.97-3.27	.062	2.31	1.20-4.45	.012
Familiarity for CAD	2.03	0.70-5.91	.192	–	–	–
Smoke	1.26	0.55-2.86	.579	–	–	–

OR indicates odds ratio.

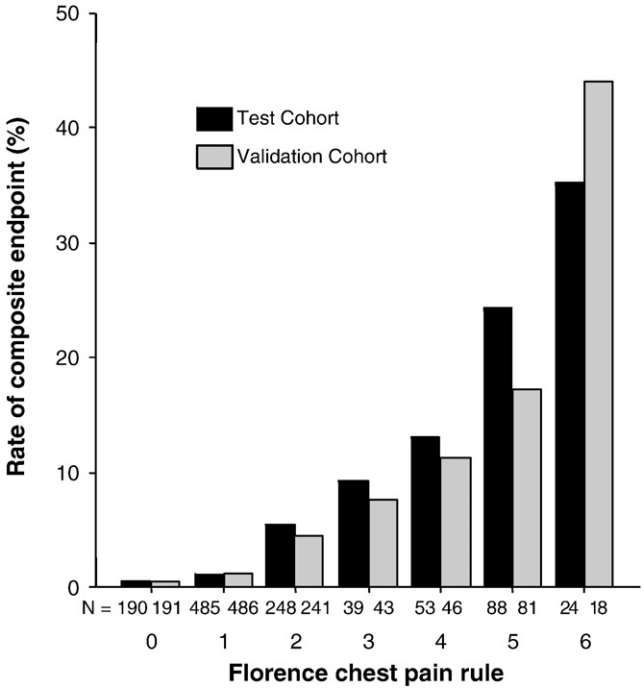

Fig. 2 Clinical variables considered in patients enrolled in the study and correlation with the rate of the composite end point.

rate as the Florence prediction rule increased in the test cohort (149, $P < .001$). The *C* statistic for the model in the test cohort was 0.83 (95% CI, 0.77-0.88; $P = .029$).

3.2. Validation of the Florence prediction rule

The validation cohort was represented by the remaining patients (n = 1127). At 6-month follow-up, 4.7% reached the composite end point (Table 2). When patients of the validation cohort were stratified, there is a progressive significant pattern of increasing event rate as the Florence prediction rule increased ($P < .001$). The validation cohort presented a homogenous pattern with the test cohort as the slope of the increase in event rates in comparison with the increase in the score of the Florence prediction rule was not statistically significant (slope of test cohort of 5.71 vs slope of validation cohort of 6.05, $P = .853$) in the 2 cohorts (Fig. 2). The *C* statistic for the model in the validation cohort was 0.81, not significantly different from the test cohort ($P = .649$).

3.3. Exploring potential clinical impact of the Florence prediction rule

To explore the potential impact of the present prediction rule in the clinical practice, we first categorized patients with low-risk CP into 3 risk group: group A, prediction rule 0 or 1 (n = 1352, 61%); group B, prediction rule 2 to 4 (n = 670, 30%); and group C, prediction rule 5 or 6 (n = 211, 9.5%). Patients in group A showed a very low incidence of composite end point (1%), whereas patients in group C showed an unexpected very high incidence of the end point (24.6%) in face of the initial recognition of patients with low-risk CP (C vs A, $P < .001$). The sensitivity, specificity, and predictive values are shown in Table 4. As shown in Fig. 3, in our test cohort, we found a progressive significant ($P < .001$) increase of the composite end point of up to 24.6%, in both myocardial infarction and revascularization. In particular, the rate of myocardial infarction increased from almost 0% in group A to 4% in group C, thus identifying 2 extreme risk groups. A similar incidence rate for each of the end points was found in the validation cohort.

3.4. The potential usefulness of the Florence prediction rule

To investigate the potential usefulness of the prediction rule for screening patients with CP in the CP unit, we conducted a post hoc analysis restricted to the population submitted to ETT (n = 798), by comparing the prognostic yield of the prediction rule with that of ETT. First, we stratified ETT patients according to the Florence prediction rule (groups A, B, and C) and we compared the event rate in each category with negative or positive ETT. When we focused on group A (event rate, 3.6%; n = 7), only 13 of the 193 patients tested showed a positive ETT (6.7%) and only 4 (2.1%) of those reached the end point. Moreover, in the same group, only 3 (1.7%) of 180 patients with negative ETT reached the end point, similar to the pretest (3.6%). Thus, in this very low risk subgroup ETT prognostic yield may be questionable. Conversely, the patients of group C who had a negative ETT experienced an event rate of up to 17.4%, suggesting the need for higher sensitivity testing (stress

Table 4 Sensitivity, specificity, and predictive values of patients enrolled in the study and submitted to ETT

Patients with CP	Patients enrolled in the study (n = 2233)		Patients submitted to ETT (n = 798)	
	Group A	Group C	Group A	Group C
Sensitivity	0.88	0.48	0.57	0.42
Specificity	0.63	0.93	0.95	0.83
Positive predictive value	0.11	0.25	0.31	0.50
Negative predictive value	0.99	0.97	0.98	0.77
Diagnostic accuracy	0.95	0.95	0.96	0.71

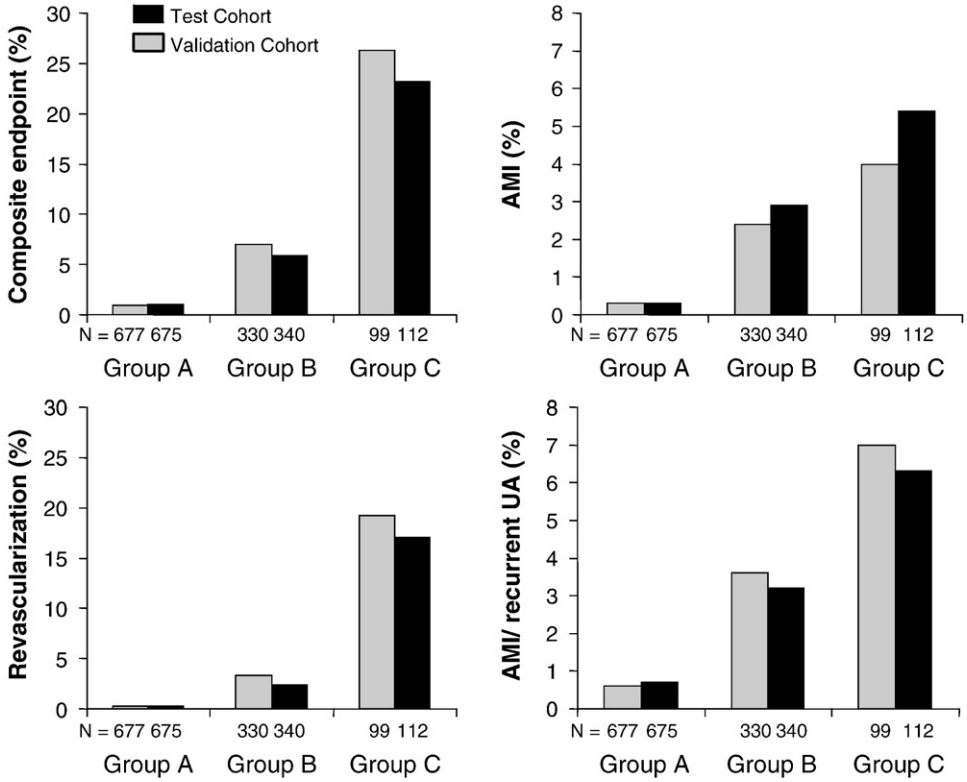

Fig. 3 Rate of coronary events including acute myocardial infarction, and revascularization in patients of the study (2233).

echocardiography, or stress nuclear imaging, or at least coronary angiography).

4. Discussion

This study showed a new simple clinical risk score, the Florence prediction rule, was accurate in stratifying the cardiovascular risk of patients with CP, without existing known coronary disease, and initial negative work-up, usually considered at low risk for future coronary events. The clinical prediction rule, composed of 5 independent prognostic variables (CP score higher than 6, male gender, age older than 50 years, MS, and DM), identifies 3 groups of patients with a risk ranging from 1% (group A, rule 0-1) to 25% (group C, rule 5-6) (Figs. 3 and 4).

The strengths of our study are as follows:

1) To our knowledge, this is the first prediction rule that is easy to use and is applicable in clinical practice for risk stratification of patients with CP and initial negative work-up.
2) Patients with a prediction rule of 1 or less belonged to a very low risk group (group A; event rate 1%) which account for 60% of the population enrolled in the study.
3) Patients with a prediction rule higher than 4 (group C) were considered at very high risk, showing an event rate of up to 25%, comparable with that of patients with unstable angina and positive troponin test.

In the past years, several multivariate algorithms have been developed in patients with CP for estimating the need of intensive care [3,5-7,31,32]. However, those studies were performed before troponin testing was routinely available, thus including patients considered at high risk, per se, to date. Thus, a prediction rule which stratifies patients considered at low risk beyond first-line work-up is still

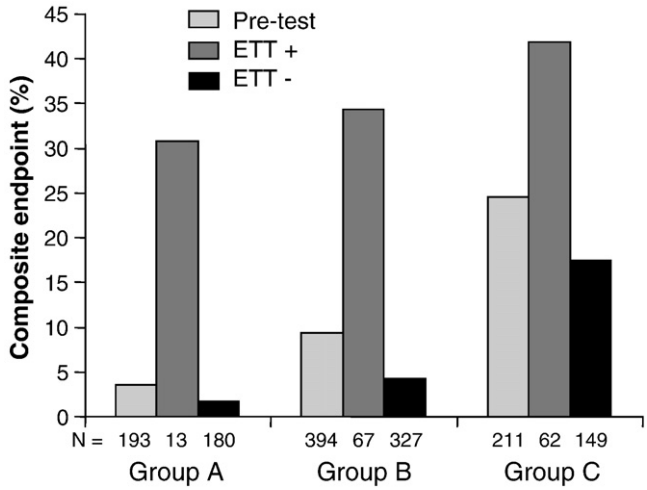

Fig. 4 Comparison of posttest likelihood with pretest likelihood in patients submitted to ETT (n = 798).

lacking. According to classical definition, our population should be considered as at low risk because they were managed with observation, serial ECGs, troponins, and echocardiography. Nonetheless, we recognized that these patients were heterogeneous; in fact, they presented with different clinical risk profiles, based on both clinical presentation and the presence of cardiovascular risk factors, and, finally, showed different outcomes. Previous risk models well stratified the overall population of patients with CP at hospital admission; however, they appeared complex to be integrated in clinical practice [3,5-7,32,33].

We sought to investigate the relationship between the presence of clinical variables that are easily detectable and adverse cardiovascular outcome. We found that cardiovascular risk factors (age >50 years, diabetes, male gender, and metabolic syndrome) together with CP clinical characteristics (CP score >6) were able to well stratify a large cohort of patients with CP and negative initial work-up (Fig. 2). Among the variables selected, the clinical characteristics of CP at presentation took a remarkable weight in the evaluation of patients with CP as the presence of CP score higher than 6 in our derivation cohort has a factor of 3, which was 3-fold higher than in the other variables, and identifies, per se, patients at substantial risk of short-term adverse coronary events (up to 6%).

The first risk group (group A) showed a very low probability of future cardiac events. Of note, in this large first group of patients, the 1% coronary event rate at follow-up is even lower than the risk reported in the same "low-risk" patients in a previous study [1,2]. Moreover, in the same very low-risk group, the low cost and worldwide availability of ETT did not substantially increase the ability in ruling out future coronary events as compared with the prediction rule (1.7% vs 3.6% event rate of the pretest). Thus, these patients could be reasonably considered for safe discharge without further investigation or managed on an outpatient basis, thus economizing on stress testing. This strategy could represent an attractive option for CP screening in the ED in a public health care delivery setting, because patients in group A of our series account for at least 21% (1352/6396) of the whole population with CP presenting to the ED and 60% (1352/2233) of patients with CP and normal ECG. On the other hand, the event rate in patients of group C is substantially the same for patients with angina and abnormal troponins, called "high-risk" patients in previous studies [19] (Fig. 4). Moreover, the rate of myocardial infarction in group C increased by up to 4%, which was 2-fold higher than that usually identified for patients with low-risk CP (<2%) [2,19]. These observations could lead to a possible implication in decision making [34]. In fact, patients in group C with negative ETT retained a high cardiovascular risk (17.4%) and should be considered for admission or further evaluation to rule out the presence of coronary disease before safe discharge. Patients with intermediate risk (group B, score 2-4) appear to be the population that could benefit from in-hospital ETT.

4.1. Study limitations

Regarding the extensibility of the study to symptomatic general population, one of the main limitations is the exclusion of patients with prior diagnosis of coronary artery disease, resting echocardiographic left ventricular dysfunction, or wall motion abnormalities. Moreover, the results obtained in our series are relative to our large teaching hospital and need validation in other centers.

Considering the potential impact of the prediction rule on a more rational use of ETT in patients with CP, we conducted a post hoc analysis on patients who underwent ETT. The preliminary results of this analysis need to be confirmed in a properly designed study. Finally, the evaluation of outcome based on dichotomy (normal/abnormal tests) may be a limitation of any screening work-up in patients with CP.

5. Conclusions

The present simple clinical prediction rule accurately predicts the risk of coronary events in patients with acute CP and normal ECG, without existing known coronary disease, and may be a valuable tool for guiding their management by a threshold approach to clinical decision making [34].

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