European Review for Medical and Pharmacological Sciences 2020; 24: 10096-10106

A nomogram to predict major adverse cardiovascular events of patients with acute chest pain, Non-ST-segment deviation, and normal troponin concentrations

Z.-N. CAO[1], K. WANG[1], G.-X. ZUO[1], M.-H. ZHANG[1], X.-G. JIA[1], Y. LI[1], C.-C. WANG[1], X.-C. ZHANG[1], X.-B. LI[2], X.-P. DU[1]

[1]Department of Cardiology, Tianjin Fifth Central Hospital, Tianjing, P.R. China
[2]Department of Cardiology, Peking University People's Hospital, Beijing, P.R. China

Abstract. – OBJECTIVE: To explore the potential indicators including patients' characteristics, electrocardiogram (ECG), echocardiography, and serological assay in predicting the major adverse cardiovascular events (MACE) within 1 year for patients with low-risk chest pain with a nomogram.

PATIENTS AND METHODS: The detected indicators of patients with low-risk chest pain were obtained as the alternative predictors for MACE. After the 1-year follow-up, patients with MACE were enrolled in the MACE group while the remained patients were in the non-MACE group. A nomogram was constructed based on the multivariable Cox regression to link the independent predictors and the MACE within 1 year for patients with low-risk chest pain.

RESULTS: The incidence of MACE within 1 year was 6.94% according to the follow-up result. Multivariate analysis revealed that risk factors of CAD, P-terminal force in lead V1 (PTFV1), C-reactive protein (CRP), and transmitral inflow early diastolic peak velocity (E wave) /peak early diastolic velocity (Em) (E/Em) were the independent predictors for the MACE. A nomogram incorporating these independent predictors with a good discrimination (0.79 in C-index) and calibration was constructed to predict the incidence of MACE within 1 year. It could be used to help select the patients with a high risk of MACE and develop preventive treatment strategies.

CONCLUSIONS: Risk factors of CAD, PTFV1, CRP, and E/Em were the independent predictors for the MACE within 1 year in patients with low-risk chest pain. The present nomogram provides a user friendly tool in the prediction of MACE for these patients.

Key Words:
Nomogram, Acute chest pain, Major adverse cardiovascular events, Electrocardiogram, Echocardiography, Serological assay.

Introduction

Patients with acute chest pain are routinely analyzed with a clinical score to receive the best management in a clinical setting[1-3]. Commonly used clinical scores [e.g., thrombolysis in myocardial infarction (TIMI) risk score] are calculated mainly based on the patients' symptoms, electrocardiogram (ECG), and serological assay[4-8].

The ST-segment deviation in ECG is helpful to judge the acute coronary syndrome (ACS) at moderate-to-high risk[9]. Troponin is a significant index for the diagnosis and risk stratification of ACS due to its high sensitivity[10]. However, some patients with acute chest pain, non-ST-segment deviation, and normal troponin are often classified as a benign etiology of chest pain because of their lower clinical scores[11]. Except for routine ECG and troponin examination, generally no further imaging or other examinations are performed for them. The routine treatment protocol is to help relieve chest pain symptoms and suggest a follow-up[12].

Recently, some studies have found an unsatisfied long-term prognosis for such patients with low-risk chest pain. Defilippi et al[13] showed that the incidence of major adverse cardiovascular events (MACE) at 1 year after discharge for the patients with acute chest pain, non-ST-segment deviation, and normal troponin was 12.8%. Sanchis et al[14] found that the incidence of acute myocardial infarction (AMI) within 1 year in these patients was 6.7%, and after 31 months of follow-up, the incidence reached 10%. These studies indicate that the patients with low-risk chest pain are mistakenly discharged from the emergency department (ED), and are still at higher risks for

Corresponding Author: Xin-ping Du, Ph.D; e-mail: duxinpingdr@163.com

MACE after a long-term follow-up, suggesting that clinical managements of such patients seem mandatory.

The present study analyzed the indicators of clinical characteristics, ECG, echocardiography, and serological assay in patients with low-risk chest pain. The aim of this study is to explore the potential indicators in predicting the MACE within 1 year for these patients with a nomogram plot, thereby helping to reduce the morbidity and mortality.

Patients and Methods

Research Participants

This prospective cohort study was approved by the Ethics Committee of Tianjin Fifth Central Hospital (TJWZXYXEC-201908). Written informed consents were obtained from all participants. A total of 424 consecutive patients with acute chest pain (including chest pain, discomfort, pressure or oppression) presenting to the ED from May 2017 to May 2018 were recruited. The inclusion criteria were as follows: (1) resting ECGs with normal ST-T changes (including 0.5 mm ST depression but not inverted T waves) were performed on arrival and at 1 h and 2 h thereafter. (2) Normal troponin T concentration was determined on arrival and at 3h thereafter. (3) Complete clinical data (including ECG, serological assay, and echocardiography) were preserved. The patients with chest pain due to aortic dissection, pulmonary embolism, arrhythmia, or trauma, and with end-stage cancer were excluded.

Collection of Patients' Characteristics

The patients' characteristics, including age, gender, coronary artery disease (CAD) risk factors (hypertension, hyperlipidemia, diabetes, family history of CAD, smoking, drinking, and obesity (body mass index (BMI) $\geq$30 kg/m^2), history of CAD, and history of ischemic stroke were collected as alternative predictors for MACE.

ECG Examination

The resting ECG pattern was recorded with patients in the supine position using PHILIPS Page Writer 300pi (Philips Healthcare, Best, Noord-Brabant, The Netherlands) (gain 10 mm/mv, paper speed 25 mm/s) (Figure 1). The ECG baseline was required to be stable and undis-

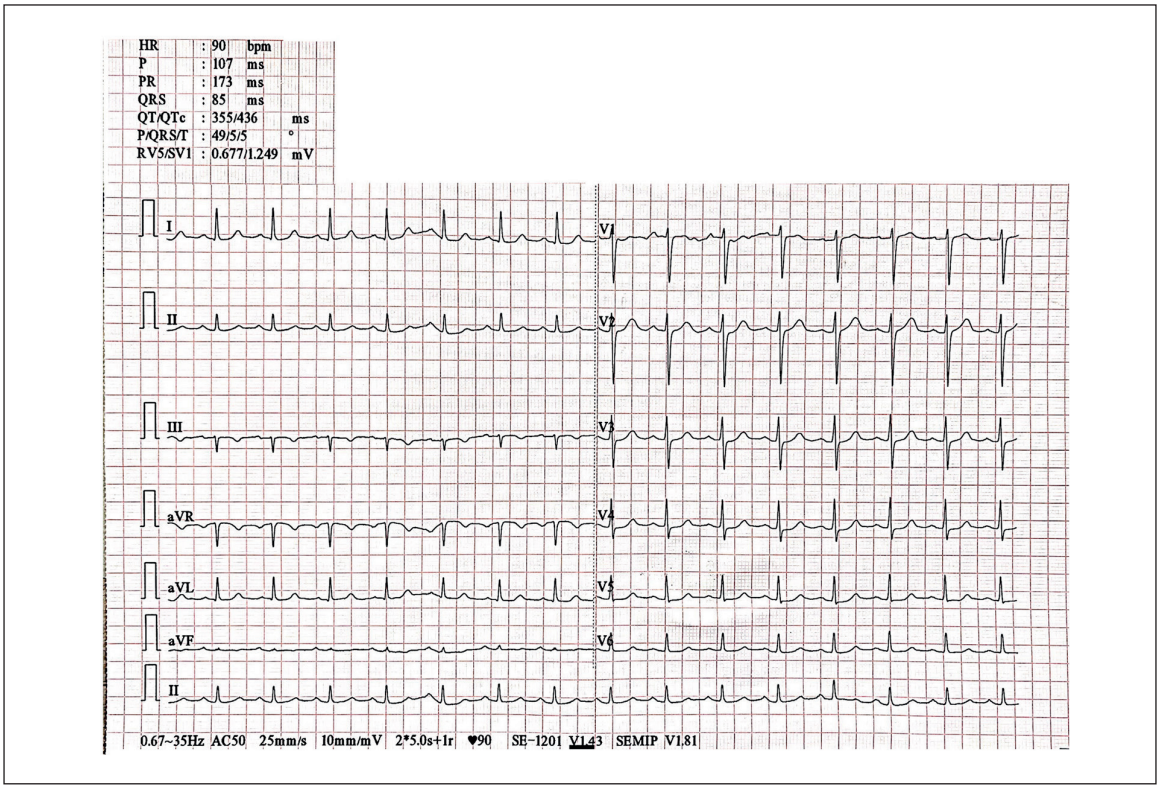

Figure 1. ECG assessment of patients with low-risk chest pain. ECG, electrocardiogram.

turbed during the examination. The indicators of ECG [heart rate, PR interval, QRS duration, and heart rate-corrected QT interval (QTc)] and the abnormal ECG performances in ventricular premature beat (VPB), P-terminal force in lead V1 (PTFV1), and left ventricular high voltage (LVH) were recorded.

Echocardiography Examination

A GE Logiq E9 ultrasonography (GE Healthcare, Madison, WI, USA) with a phased array probe (5 MHz) was used. Patients were placed in the left lateral position, and the left atrial diameter (LAD), left ventricular end-systolic diameter (LVESD), end-diastolic diameter (LVEDD), and ejection fraction (LVEF) were measured after routine cardiac scanning. Pulsed Doppler was utilized to measure the transmitral inflow early diastolic peak velocity (E wave) /late diastolic peak velocity (A wave) (E/A $\leq$ 1 indicated left ventricular diastolic dysfunction), deceleration time (DT), peak early diastolic velocity (Em), E/Em, flow propagation velocity (Vp), peak velocities during ventricular systole (S)/ early diastole (D) (S/D) and isovolumic relaxation time (IVRT) (IVRT $\leq$ -0.03 mm/s indicated abnormal) (Figure 2).

Serological Assay

COBAS E411 automatic electrochemical luminescence analyzer (Roche, Mannheim, Baden-Wurttemberg, Germany) was used to detect troponin T (cTnT), creatine kinase isoenzyme (CK-MB), and N-terminal fragment of B-type natriuretic peptide (NT-proBNP). C-reactive protein (CRP) was determined by turbidimetry (Aristo, Goldsite Diagnostics Inc., Shenzhen, P.R. China), and creatinine was assessed by COBAS c701 automatic electrochemical luminescence analyzer (Roche, Mannheim, Baden-Wurttemberg, Germany).

Follow-up

After confirmed by a negative ECG pattern and cardiac markers, the patients without recurrent chest pain 12 h after the onset or 6 h after admission were discharged and followed up once a month for 1 year (phone visit every month). During the follow-up, patients who suffered a MACE were included in the MACE group, while the remaining patients were included in the non-MACE group. Loss to follow-up was defined as non-attendance for two or more visits, or death from a disease unrelated to the study.

Statistical Analysis

Statistical product and service solutions (SPSS) (IBM, Armonk, NY, USA) software (version 22.0) and R package version 3.6.2 were used in this study. The categorical variables were expressed in number (percentage), and the Chi-square test was used for comparison. The numerical data were expressed as mean ± standard deviation for normal distribution and as medians

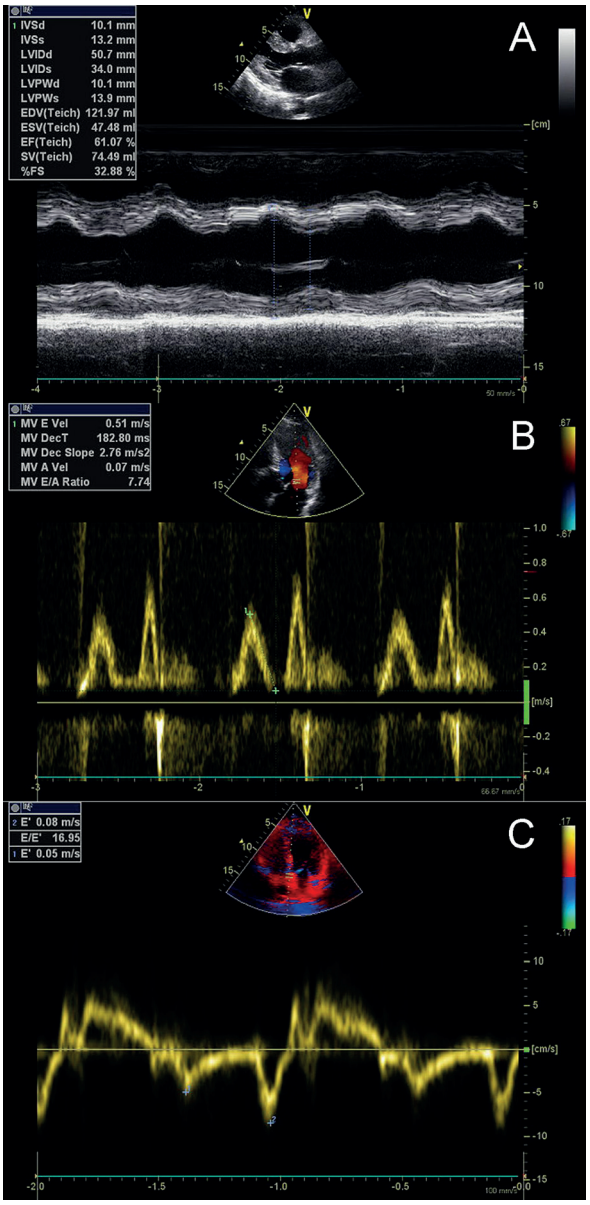

Figure 2. Echocardiographic assessment of patients with low-risk chest pain. **A,** M-mode of gray-scale ultrasound for measuring the inner chamber diameter of the heart; **B,** Pulsed-wave Doppler for evaluating blood flow information in the heart cavity; **C,** Tissue Doppler for evaluating the myocardial motion.

(interquartile range, IQR) for others. Differences between the groups were analyzed with independent samples *t*-tests for normal distribution or with the independent samples Mann Whitney U test for skewed distribution. Analysis of the follow-up was performed using Kaplan-Meier. Multivariable Cox regression was built to link the predictors that were significant at $p < 0.05$ in the univariate analysis and the MACE within 1 year. The hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated and served as the basis of the nomogram. The performance of the nomogram was assessed by Harrell's concordance index (C-index)[15]. Bootstrap resampling (1,000 times) was used for internal validation[16]. Then, calibration plots for the incidence of MACE were plotted to compare the predicted and observed incidence after the bias correction of bootstrap resampling.

Results

Follow-up Results

At the end of the follow-up, 29 patients with MACE were included in the MACE group, while the remaining 389 patients without MACE at the end of the follow-up were included in the non-MACE group (6 patients were lost to follow-up). Figure 3 shows that the incidence of MACE within 1 year was 6.94 %.

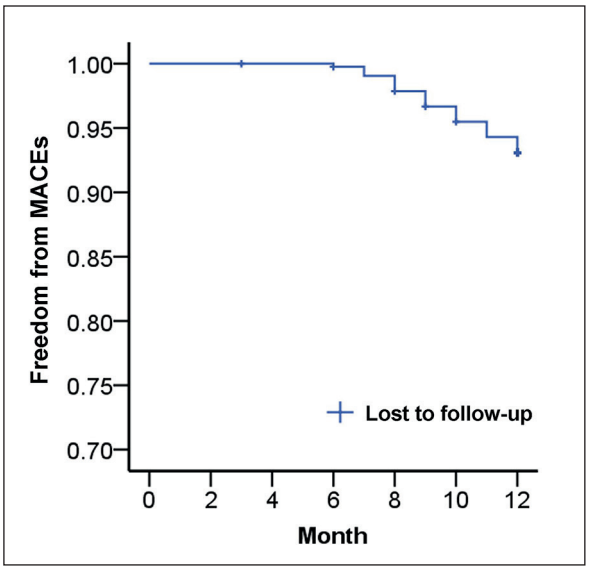

Figure 3. Incidence of MACE within 1 year for patients with acute chest pain, non-ST-segment deviation, and normal troponin concentrations. MACE, major adverse cardiovascular events.

Differences Between the MACE Group and non-MACE Group

In the patients' characteristics, the proportion of risk factors of CAD and history of CAD differed between the two groups ($p < 0.05$). About 70% of patients in the MACE group combined 3 or 4 CAD risk factors, whereas about 60% of patients in the non-MACE group combined 2 or 3 CAD risk factors (Table I). In the ECG indicators, the proportions of VPB, QTc, and PTFV1 in the MACE group were higher than in the non-MACE group ($p < 0.05$, Table II). Of them, the difference of PTFV1 between the two groups was relatively significant. In the serological indicators, CRP in the MACE group was higher than in the non-MACE group ($p < 0.05$, Table III). In the echocardiography indicators, IVRT and E/Em in the MACE group were higher than in the non-MACE group ($p < 0.05$, Table IV).

Multivariate Analysis for the Alternative Predictors Associated with the MACE Within 1 year

The results of the univariate analysis indicated that patients with multiple risk factors including risk factors of CAD, VPB, QTc, PTFV1, CRP, IVRT, and E/Em had a higher risk of MACE within 1 year. Multivariate analysis further revealed that risk factors of CAD, PTFV1, CRP, and E/Em remained as the independent predictors for the MACE (Table V). A nomogram incorporating the independent predictors was constructed to predict the risk of MACE within 1 year (Figure 4).

Validation of the Nomogram

Figure 5 shows that the prediction model had a bia-corrected C-index of 0.79 (95% CI: 0.70-0.87), which indicated a good discrimination (> 0.75). Figure 6 shows that no significant difference was observed between the predicted percentages and the observed probabilities of MACE within 1 year, which demonstrated a good calibration between the prediction by nomogram and the actual observation.

Utility of the Nomogram

The nomogram could be utilized to calculate the scores corresponding to each independent predictor of MACE, and the predicted probability corresponding to the sum of the scores was the risk of patients suffering MACE within 1 year. It could help select the patients with a high risk of MACE and develop preventive treatment strategies. For example, when a patient with acute chest

Table I. Comparison of the patients' characteristics between the MACE group and non-MACE group.

Variables		MACE group (n = 29)	Non-MACE group (n = 389)	t/χ^2 value	*p* value
Age (years)		57.31 ± 10.89	54.75 ± 8.22	1.578	0.115
Gender	Male	16 (55.2%)	161 (41.4%)	2.100	0.147
	Female	13 (44.8%)	228 (58.6%)		
Smoking	Yes	15 (51.7%)	172 (44.2%)	0.615	0.433
	No	14 (48.3%)	217 (55.8%)		
Alcohol consumption	Yes	15 (51.7%)	182 (46.8%)	0.024	0.877
	No	14 (48.3%)	207(53.2%)		
BMI	> 30 kg/m^2	16 (55.2%)	151 (38.8%)	3.009	0.083
	≤ 30 kg/m^2	13 (44.8%)	238 (61.2%)		
Family history of CAD	Yes	17 (58.6%)	180 (46.3%)	1.651	0.199
	No	12 (41.4%)	209 (53.7%)		
Diabetes mellitus	Yes	19 (65.5%)	205 (52.7%)	1.783	0.182
	No	10 (34.5%)	184 (47.3%)		
Hypertension	Yes	18 (62.1%)	186 (47.8%)	1.058	0.304
	No	11 (37.9%)	203 (52.2%)		
Hyperlipidemia	Yes	17 (58.6%)	189 (48.6%)	1.087	0.297
	No	12 (41.4%)	200 (51.4%)		
Risk factors of CAD	1	1 (3.4%)	19 (4.9%)	16.867	0.005
	2	2 (6.9%)	135 (34.7%)		
	3	9 (31.0%)	128 (32.9%)		
	4	12 (41.4%)	63 (16.2%)		
	5	3 (10.3%)	27 (6.9%)		
	6	2 (6.9%)	17 (4.4%)		
	7	0 (0%)	0 (0%)		
Ischemic stroke	Yes	12 (41.4%)	135 (34.7%)	0.527	0.468
	No	17 (58.6%)	254 (65.3%)		
History of CAD	Yes	16 (55.2%)	180 (46.3%)	0.858	0.354
	No	13 (44.8%)	209 (53.7%)		

BMI, body mass index; CAD, coronary artery disease; MACE, major adverse cardiovascular events.

pain, non-ST-segment deviation, and normal troponin concentrations is combined with 4 CAD risk factors, abnormal PTFV1, 5 mg/L in CRP, and 6 in E/Em, the total score is about 165, which indicated that the probability of MACE within 1 year is about 15%. Clinicians can choose some appropriate treatments according to the result to avoid an inappropriate discharge from the ED.

Table II. Comparison of the ECG indicators between the MACE group and non-MACE group.

Variables		MACE group (n = 29)	Non-MACE group (n = 389)	t/χ^2 value	*p* value
Heart rate (bpm)		78.93±8.41	75.99 ± 8.20	1.857	0.064
QRS duration	Prolonged	2 (6.9%)	21 (5.4%)	0.116	0.733
	Normal	27 (93.1%)	368 (94.6%)		
PR interval	Prolonged	3 (10.3%)	35 (9.0%)	0.059	0.808
	Normal	26 (89.7%)	354 (91.0%)		
VPB	Yes	11 (37.9%)	85 (21.9%)	3.944	0.047
	No	18 (62.1%)	304 (78.1%)		
QTc	Prolonged	8 (27.6%)	53 (13.6%)	4.189	0.040
	Normal	21 (72.4%)	336 (86.4%)		
PTFV1	Abnormal	9 (31.0%)	59 (15.2%)	5.318	0.026
	Normal	20 (69.0%)	330 (84.8%)		
LVH	Yes	10 (34.5%)	117 (30.1%)	0.248	0.619
	No	19 (65.5%)	272 (69.9%)		

LVH, left ventricular high voltage; MACE, major adverse cardiovascular events; PTFV1, P-terminal force in lead V1; QTc, corrected QT interval; VPB, ventricular premature beat.

Table III. Comparison of the serological indicators between the MACE group and non-MACE group.

Variables	MACE group (n = 29)	Non-MACE group (n = 389)	t/χ^2 value	*p* value
CK-MB (ng/mL)	2.84 ± 1.36	2.48 ± 1.02	1.757	0.080
cTnT (μg/L)	0.029 ± 0.019	0.027 ± 0.018	0.528	0.598
NT-proBNP (ng/L)	92.73 ± 33.28	95.21 ± 34.56	0.525	0.600
CRP (mg/L)	3.03 (1.40, 4.43)	2.07 (0.96, 3.33)	4201	0.022
Creatinine (mol/L)	77.95 ± 22.76	72.23±24.48	0.461	0.645

CK-MB, creatine kinase isoenzyme; cTnT, troponin T; CRP, C-reactive protein; MACE, major adverse cardiovascular events; NT-proBNP, N-terminal fragment of B-type natriuretic peptide.

Table IV. Comparison of the echocardiography indicators between the MACE group and non-MACE group.

Variables	MACE group (n = 29)	Non-MACE group (n = 389)	t/χ^2 value	*p* value
LVEF (%)	61.22 ± 4.33	60.25 ± 2.90	-1.193	0.233
LVEDD (mm)	50.06 ± 4.92	49.19 ± 3.60	1.224	0.222
LVESD (mm)	34.10 ± 3.18	33.94 ± 4.34	0.203	0.839
IVRT (ms)	134.43 (122.96, 153.76)	128.02 (111.39, 144.73)	4306.5	0.034
E/A	1.27 (1.18, 1.39)	1.21 (1.06, 1.33)	4486	0.063
LAD (mm)	34.95 (31.97, 37.81)	33.93 (31.23, 36.35)	4550	0.082
DT (ms)	203.64 ± 29.23	209.91 ± 33.19	-0.989	0.323
E/Em	5.08 (3.84, 6.73)	4.30 (3.50, 5.30)	4091.5	0.014
Vp (cm/s)	42.96 (39.48, 45.84)	44.68 (40.19, 48.11)	4676	0.124
S/D	1.00 (0.83, 1.26)	1.15 (0.90, 1.45)	4454	0.059

E/A, transmitral inflow early diastolic peak velocity (E wave) /late diastolic peak velocity (A wave); DT, deceleration time; E/Em, transmitral inflow early diastolic peak velocity (E wave) /peak early diastolic velocity (Em); IVRT, isovolumic relaxation time; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; S/D, peak velocities during ventricular systole (S)/ early diastole (D); Vp, flow propagation velocity.

Discussion

Patients with acute chest pain, non-ST-segment deviation, and normal troponin concentrations are often evaluated as low-risk chest pain by commonly used clinical scores. However, these patients will still have a chance to suffer MACE in the future. In the present study, a 1-year follow-up was performed for them considering that a long-term follow-up will lead to more interferences that may reduce the accuracy of potential indicators in predicting the MACE of patients

Table V. Independent predictors of MACE within 1 year in patients with low-risk chest pain.

Variables LVEF (%)	Multivariable analysis		*p*
	HR	95% CI	
Risk factors of CAD	1.577	1.163-2.138	0.003
VPB	2.214	0.663-7.395	0.196
QTc	1.582	0.795-3.861	0.147
PTFV1	2.337	1.321-4.762	0.028
CRP	1.267	1.014-1.582	0.037
IVRT	1.017	0.934-1.035	0.076
E/Em	1.464	1.131-1.896	0.004

CAD, coronary artery disease; E/Em, transmitral inflow early diastolic peak velocity (E wave) / peak early diastolic velocity (Em); CRP, C-reactive protein; IVRT, isovolumic relaxation time; PTFV1, P-terminal force in lead V1; QTc, corrected QT interval; VPB, ventricular premature beat.

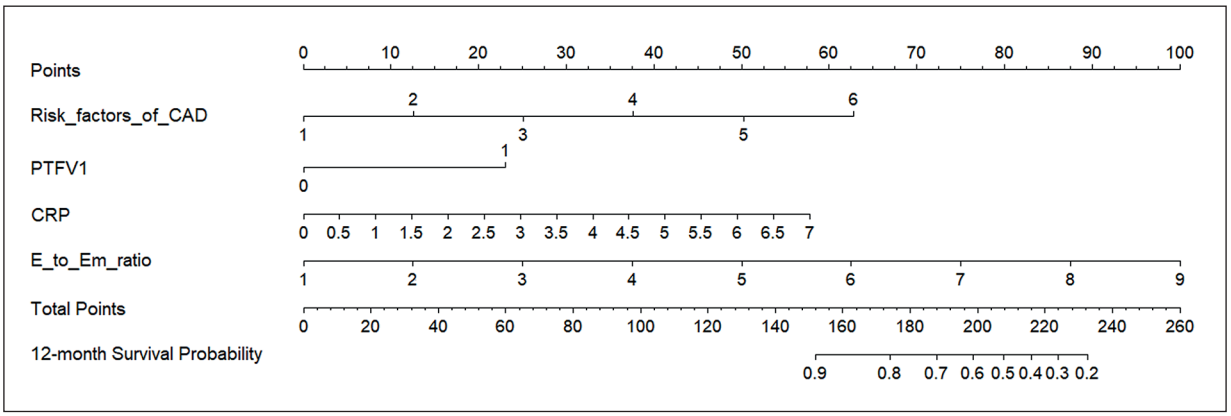

Figure 4. The nomogram incorporating the risk factors of CAD, PTFV1, CRP, and E/Em to predict the incidence of MACE within 1 year in patients with acute chest pain, non-ST-segment deviation, and normal troponin concentrations. The nomogram can be used to obtain the probability of MACE within 1 year by adding up the points identified on the point scale for each variable. MACE, major adverse cardiovascular events; CAD, coronary artery disease; PTFV1, P-terminal force in lead V1; CRP, C-reactive protein; E/Em, transmitral inflow early diastolic peak velocity (E wave) /peak early diastolic velocity (Em).

with low-risk chest pain. The result of follow-up showed that the incidence of MACE within 1 year was 6.94%, which was similar to the study by Sanchis et al[14]. It suggested that a prognostic assessment of patients with low-risk chest pain seems mandatory.

Low-risk Chest Pain Patients with Multiple CAD Risk Factors (≥ 3) Associated with an Increased Risk of MACE

In our study, approximately 70% of patients with MACE within 1 year combined with 3 or 4 CAD risk factors while the proportion of 2 or 3 CAD risk factors was the majority (60%) in the patients without MACE. These patients presenting to the ED were evaluated as low-risk chest pain by TIMI score (0-2 points)[17]. Multivariable Cox regression showed that each increase in CAD risk factors was associated with an approximately 60% increase in the risk of MACE. It suggested that for patients with low-risk chest pain, appropriate interventions to avoid future MACE seems necessary when combining multiple CAD risk factors (≥ 3), even if their clinical scores at admission are low.

Low-risk Chest Pain Patients with Left Ventricular Diastolic Dysfunction Associated with an Increased Risk of MACE

Besides CAD risk factors, our study revealed that E/Em, PTFV1, and CRP were independently associated with an increased risk of MACE within 1 year in patients with low-risk chest pain. It implied that the prognostic evaluation of these patients must be completed using assessments that are not routinely used in ED. Abnormal E/Em and PTFV1 could be present in patients with left ventricular diastolic dysfunction, which might be associated with a MACE in the future. Nowadays researchers have gradually recognized that left ventricular diastolic dysfunction is also one of the leading causes of coronary heart disease[18].

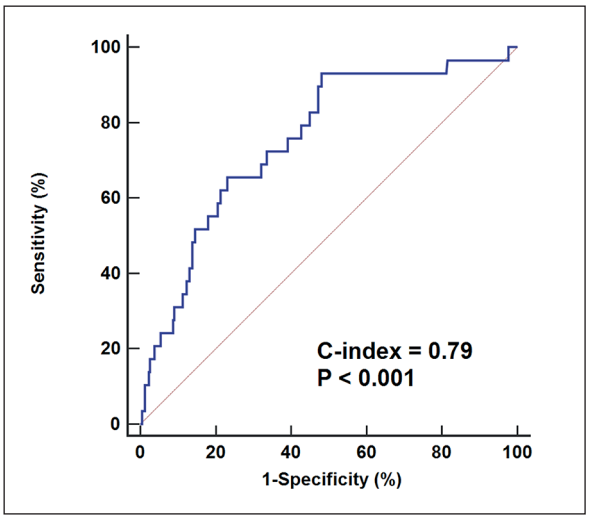

Figure 5. The receiver operating characteristic curve (ROC) for the discrimination of the nomogram to predict MACE within 1 year in patients with low-risk chest pain. The C-index (i.e., area under receiver operating characteristic curve) is 0.79 (95% CI: 0.70 - 0.87). MACE, major adverse cardiovascular events.

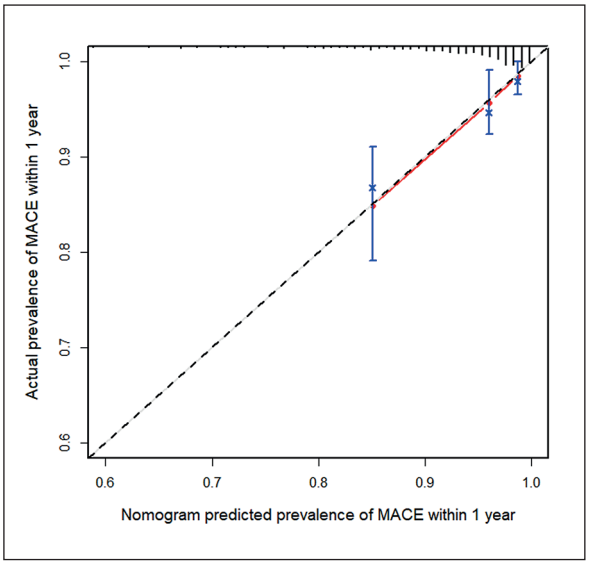

Figure 6. The calibration curves for predicting the incidence of MACE within 1 year. The red line along the dashed line indicates that the predicted prevalence is close to the actual prevalence. MACE, major adverse cardiovascular events.

Myocardial ischemia and its early pathological changes often first damage left ventricular diastolic function[19,20]. Therefore, the early detection of left ventricular diastolic dysfunction can help improve the prognosis of CAD patients.

PTFV1 has been used extensively for the early diagnosis of chronic heart failure and the evaluation of its prognosis[21,22]. It is associated with the range of myocardial ischemia and the severity of CAD[23]. Williamson et al[24] reported that the changes of PTFV1 in patients with non-ST-segment elevation ACS during hospitalization may indicate the degree of influence of myocardial ischemia. In our study, the estimated hazard ratio of MACE was approximately 1.9 times higher for patients with abnormal PTFV1 than for those with normal PTFV1.

E/Em was valuable for the prediction of the adverse events under various pathological conditions such as AMI, hypertension heart disease, validated functional mitral regurgitation, and atrial fibrillation[25]. Among patients without demonstrable myocardial ischemia, increased E/Em was associated with higher cardiovascular events over a long-term follow-up[26]. In our study, E/Em was the only echocardiographic indicator that could independently predict the occurrence of MACE. Each point increase in E/Em was associated with an approximately 50% increase in the risk of MACE.

Detection of CRP in Patients with Low-Risk Chest Pain Help Identifying Potential MACE

It is well known that CRP is a sensitive, non-specific, and systemic marker of inflammation and infection. Recent studies have revealed a consistent association between atherothrombotic disease and CRP[27]. It may appear in the atherosclerotic lesion and its elevation helps to indicate the degree of atherosclerosis and local inflammation caused by the rupture of unstable plaques[28]. On the other hand, increased CRP may be caused by inflammation in other parts of the body[29]. This chronic low-grade inflammation (e.g., rheumatoid arthritis) may lead to atherosclerosis and may be associated with an increased risk of CAD[30]. Some studies have utilized CRP to evaluate the risk of cardiovascular disease in asymptomatic middle-aged or elderly population. CRP enhances the global coronary risk and might have implications for future risk assessments[31,32]. At present, CRP has not been used as a routine detection index for acute chest pain. However, CRP has a special diagnostic and prognostic value for patients with acute chest pain[33,34]. Especially when troponin concentrations and ECG are normal in patients with chest pain presenting to the ED, CRP plays an important role in the risk stratification[35]. In our research, CRP was an independent predictor of MACE in patients with low-risk chest pain, indicating that the detection of CRP may help to identify potential MACE in the future.

Nomogram as a Convenient Tool for Predicting MACE

The routinely used clinical scores cannot predict the long-term risk of MACE in patients with low-risk chest pain. The nomogram built on the multiple independent predictors has been identified as a useful and convenient tool for disease prediction. Therefore, we plotted and verified a nomogram to overcome the shortage of clinical scores as a means of MACE prediction and management guidance for patients with low-risk chest pain. The present nomogram derived from the collected data of patients' characteristics, ECG, echocardiography, and serological assay was shown to identify the patients with low-risk chest pain who may suffer MACE within 1 year. Moreover, the plotted nomogram showed a good discrimination (about 0.8 in C-index), and the calibration plot implied a good fit. When a patient with low-risk chest pain is ready to be discharged from the ED. It is useful to consult this

nomogram whether the patient has the risk of MACE within 1 year. By using this nomogram, the decision-making regarding the management of patients with low-risk chest pain is hoped to be improved. Due to the limitation of the number of cases and single-center study, the nomogram has not been externally verified and the prediction accuracy in different populations still needs to be verified in further studies. We believe that the predictive value of the nomogram will be further improved with more multi-center clinical researches participated.

Conclusions

Shortly, in patients with acute chest pain, non-ST-segment deviation, and normal troponin concentrations, our study revealed that the risk factors of CAD, PTFV1, E/Em, and CRP were independently associated with an increased risk of MACE within 1 year. The decision-making regarding the management of such patients may be improved by using the developed nomogram. The nomogram represents an accurate and user-friendly model for predicting MACE. It is important for individualized and accurate prediction of the prognosis of patients with low-risk chest pain.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

The authors wish to thank all the study participants, research staff and students who participated in this work.

Funding

This study was supported by the key supporting projects of Tianjin Binhai New Area Health Committee(2019BWKZ005).

Contributorship Statement

ZC, KW and XD designed the research. ZC, KW, GZ, MZ, XJ, YL, CW, and XZ performed the research. XZ, XL and XD contributed new analytic tools. GZ, MZ, XJ, YL, CW, XZ, and XL analyzed data. ZC, KW, GZ, and XD were major contributors in writing the manuscript. All authors read and approved the final manuscript.

References

1) De Venecia TA, Lu MY, Nwakile CC, Figueredo VM. Utility of the QT interval in predicting outcomes in patients presenting to the emergency department with chest pain. Coron Artery Dis 2015; 26: 422-424.
2) Dubin J, Kiechle E, Wilson M, Timbol C, Bhat R, Milzman D. Mean HEART scores for hospitalized chest pain patients are higher in more experienced providers. Am J Emerg Med 2017; 35: 122-125.
3) Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax Jj, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016; 37: 267-315.
4) Backus BE, Six AJ, Kelder JC, Bosschaert MA, Mast EG, Mosterd A, Veldkamp RF, Wardeh AJ, Tio R, Braam R, Monnink SH, Van Tooren R, Mast TP, Van Den Akker F, Cramer MJ, Poldervaart JM, Hoes AW, Doevendans PA. A prospective validation of the HEART score for chest pain patients at the emergency department. Int J Cardiol 2013; 168: 2153-2158.
5) Huffman JC, Beale EE, Beach SR, Celano CM, Belcher AM, Moore SY, Suarez L, Gandhi PU, Motiwala SR, Gaggin H, Januzzi JL. Design and baseline data from the Gratitude Research in Acute Coronary Events (GRACE) study. Contemp Clin Trials 2015; 44: 11-19.
6) Poldervaart JM, Langedijk M, Backus BE, Dekker IMC, Six AJ, Doevendans PA, Hoes AW, Reitsma JB. Comparison of the GRACE, HEART and TIMI score to predict major adverse cardiac events in chest pain patients at the emergency department. Int J Cardiol 2017; 227: 656-661.
7) Roy SS, Abu Azam STM, Khalequzzaman M, Ullah M, Arifur Rahman M. GRACE and TIMI risk scores in predicting the angiographic severity of non-ST elevation acute coronary syndrome. Indian Heart J 2018; 70 Suppl 3: S250-s253.
8) Reaney PD, Elliott HI, Noman A, Cooper JG. Risk stratifying chest pain patients in the emergency department using HEART, GRACE and TIMI scores, with a single contemporary troponin result, to predict major adverse cardiac events. Emerg Med J 2018; 35: 420-427.
9) Song C, Fu R, Li S, Yang J, Wang Y, Xu H, Gao X, Liu J, Liu Q, Wang C, Dou K, Yang Y. Simple risk score based on the China Acute Myocardial Infarction registry for predicting in-hospital mortality among patients with non-ST-segment elevation myocardial infarction: results of a prospective observational cohort study. BMJ Open 2019; 9: e030772.

10) Khan MH, Islam MN, Aditya GP, Islam MZ, Bhuiyan AS, Saha B, Bhowmick K, Hassan M, Paul PK, Chowdhury S, Rahman R. Correlation of Troponin-I level with left ventricular ejection fraction and in-hospital outcomes after first attack of Non-ST segment elevation myocardial infarction. Mymensingh Med J 2017; 26: 721-731.

11) Sanchis J, Bodí V, Núñez J, Bosch MJ, Bertomeu-González V, Consuegra L, Santas E, Gómez C, Bosch X, Chorro FJ, Llàcer A. A practical approach with outcome for the prognostic assessment of non-ST-segment elevation chest pain and normal troponin. Am J Cardiol 2007; 99: 797-801.

12) Henrikson CA, Howell EE, Bush De, Miles JS, Meininger GR, Friedlander T, Bushnell AC, Chandra-Strobos N. Chest pain relief by nitroglycerin does not predict active coronary artery disease. Ann Intern Med 2003; 139: 979-986.

13) Defilippi CR, Tocchi M, Parmar RJ, Rosanio S, Abreo G, Potter MA, Runge MS, Uretsky BF. Cardiac troponin T in chest pain unit patients without ischemic electrocardiographic changes: angiographic correlates and long-term clinical outcomes. J Am Coll Cardiol 2000; 35: 1827-1834.

14) Sanchis J, Bodí V, Núñez J, Bertomeu-González V, Gómez C, Bosch MJ, Consuegra L, Bosch X, Chorro FJ, Llàcer A. New risk score for patients with acute chest pain, non-ST-segment deviation, and normal troponin concentrations: a comparison with the TIMI risk score. J Am Coll Cardiol 2005; 46: 443-449.

15) Harrell FE, Jr., Califf RM, Pryor DB, Lee KL, Rosati RA. Evaluating the yield of medical tests. Jama 1982; 247: 2543-2546.

16) Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996; 15: 361-387.

17) Antman EM, Cohen M, Bernink PJ, Mccabe CH, Horacek T, Papuchis G, Mautner B, Corbalan R, Radley D, Braunwald E. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. Jama 2000; 284: 835-842.

18) Ommen SR. Echocardiographic assessment of diastolic function. Curr Opin Cardiol 2001; 16: 240-245.

19) Brutsaert DL, Rademakers FE, Sys SU, Gillebert TC, Housmans PR. Analysis of relaxation in the evaluation of ventricular function of the heart. Prog Cardiovasc Dis 1985; 28: 143-163.

20) Dawson JR, Gibson DG. Left ventricular filling and early diastolic function at rest and during angina in patients with coronary artery disease. Br Heart J 1989; 61: 248-257.

21) Josephson ME, Kastor JA, Morganroth J. Electrocardiographic left atrial enlargement. Electrophysiologic, echocardiographic and hemodynamic correlates. Am J Cardiol 1977; 39: 967-971.

22) Ikram H, Drysdale P, Bones PJ, Chan W. The non-invasive recognition of left atrial enlargement: comparison of electro- and echocardiographic measurements. Postgrad Med J 1977; 53: 356-359.

23) Li Q, Gu LD, Zhang C, Liu W, Peng Y, Chai H, Xu YN, Wei JF, Chen M, Huang DJ. A predictive study of the dynamic development of the P-wave terminal force in lead V1 in the electrocardiogram in relation to long-term prognosis in Non-ST-segment elevation acute coronary syndrome patients during hospitalization. Ann Noninvasive Electrocardiol 2015; 20: 542-553.

24) Williamson BD, Lim MJ, Buda AJ. Transient left ventricular filling abnormalities (diastolic stunning) after acute myocardial infarction. Am J Cardiol 1990; 66: 897-903.

25) Gecmen C, Candan O, Kahyaoglu M, Kalayci A, Cakmak EO, Karaduman A, Izgi IA, Kirma C. Echocardiographic assessment of right ventricle free wall strain for prediction of right coronary artery proximal lesion in patients with inferior myocardial infarction. Int J Cardiovasc Imaging 2018; 34: 1109-1116.

26) Gharacholou SM, Scott CG, Takahashi PY, Nkomo VT, Mccully RB, Fine NM, Pellikka PA. Left ventricular diastolic function and long-term outcomes in patients with normal exercise echocardiographic findings. Am J Cardiol 2013; 112: 200-207.

27) Tanveer S, Banu S, Jabir NR, Khan MS, Ashraf GM, Manjunath NC, Tabrez S. Clinical and angiographic correlation of high-sensitivity C-reactive protein with acute ST elevation myocardial infarction. Exp Ther Med 2016; 12: 4089-4098.

28) Bouki KP, Katsafados MG, Chatzopoulos DN, Psychari SN, Toutouzas KP, Charalampopoulos AF, Sakkali EN, Koudouri AA, Liakos GK, Apostolou TS. Inflammatory markers and plaque morphology: an optical coherence tomography study. Int J Cardiol 2012; 154: 287-292.

29) Koenig W, Sund M, Fröhlich M, Fischer HG, Löwel H, Döring A, Hutchinson WL, Pepys MB. C-Reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. Circulation 1999; 99: 237-242.

30) Diederichsen MZ, Diederichsen SZ, Mickley H, Steffensen FH, Lambrechtsen J, Sand NPR, Christensen KL, Olsen MH, Diederichsen A, Grønhøj MH. Prognostic value of suPAR and hs-CRP on cardiovascular disease. Atherosclerosis 2018; 271: 245-251.

31) Cushman M, Arnold AM, Psaty BM, Manolio TA, Kuller LH, Burke GL, Polak JF, Tracy RP. C-reactive protein and the 10-year incidence of coronary heart disease in older men and women: the cardiovascular health study. Circulation 2005; 112: 25-31.

32) Koenig W, Löwel H, Baumert J, Meisinger C. C-reactive protein modulates risk prediction based on

the Framingham Score: implications for future risk assessment: results from a large cohort study in southern Germany. Circulation 2004; 109: 1349-1353.

33) Potsch AA, Siqueira Filho AG, Tura BrR Gamarski R, Bassan R, Nogueira MV, Moutinho MA, Silva AC, Villacorta H, Campos Al. C-reactive protein diagnostic and prognostic value in patients presenting at the emergency room with chest pain. Arq Bras Cardiol 2006; 87: 275-280.

34) Diercks DB, Kirk JD, Naser S, Turnipseed S, Amsterdam EA. Value of high-sensitivity C-reactive protein in low risk chest pain observation unit patients. Int J Emerg Med 2011; 4: 37.

35) Kavsak PA, Macrae AR, Newman AM, Lustig V, Palomaki GE, Ko DT, Tu JV, Jaffe AS. Elevated C-reactive protein in acute coronary syndrome presentation is an independent predictor of long-term mortality and heart failure. Clin Biochem 2007; 40: 326-329.