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Prognostic value of neutrophil gelatinase-associated lipocalin and glycosylated hemoglobin for non-ST-segment elevation myocardial infarction patients with single concomitant chronic total occlusion following primary percutaneous coronary intervention

A prospective observational study

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Abstract

To investigate factors predicting the onset of major adverse cardiovascular and cerebrovascular events (MACCEs) after primary percutaneous coronary intervention (pPCI) for patients with non-ST-segment elevation infarction (NSTEMI) and single concomitant chronic total occlusion (CTO). Neutrophil gelatinase-associated lipocalin (NGAL) and glycosylated hemoglobin (HbA1c) both play essential role in cardiovascular and cerebrovascular homoeostasis. However, current knowledge of its predictive prognostic value is limited.

422 patients with NSTEMI and CTO (59.7 ± 12.4 years, 74.2% men) who underwent successful pPCI were enrolled and followed for 2 years. Multivariate cox regression analysis and receiver operating characteristic (ROC) curve analysis were performed to determine the factors predicting MACCEs.

140 patients (33.2%) experienced MACCEs in the follow-up period. Multivariate cox regression analysis found when we process the model with NGAL at admission, low left ventricular ejection fraction (LVEF, HR = 0.963, 95% CI 0.940 to 0.987, $P = .003$) and fasting blood glucose (HR = 1.078, 95% CI 1.002 to 1.159, $P = .044$), but not NGAL at admission, were independent predictors of 2 years MACCEs. While HbA1C (HR = 1.119, 95% CI 1.014 to 1.234, $P = .025$), LVEF (HR = 0.963, 95% CI 0.939 to 0.987, $P = .003$), estimated glomerular filtration rate (HR = 1.020, 95% CI 1.006 to 1.035, $P = .006$) and NGAL value 7 day (HR = 1.020, 95% CI 1.006 to 1.035, $P = .006$) showed their predictive value in another model. ROC analysis indicated NGAL 7 day (AUC = 0.680, $P = .0054$ and AUC = 0.622, $P = .0005$) and LVEF (AUC = 0.691, $P = .0298$ and AUC = 0.605, $P = .0021$) could predict both in-hospital and 2 years MACCEs, while higher NGAL at admission could only predict poorer in-hospital prognosis (AUC = 0.665, $P = .0103$). Further analysis showed the prognostic value of NGAL was particularly remarkable among those HbA1C < 6.5%.

Patients with NSTEMI and single concomitant CTO receiving pPCI with higher NGAL on 7 days during hospitalization are more likely to suffer 2 years MACCEs, particularly in those with lower HbA1C.

Abbreviations: AMI = acute myocardial infarction, AUC = area under curve, CIs = confidence intervals, CTO = chronic total occlusion, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, ESC = European Society of Cardiology, FBG = fasting blood glucose, GPI = Glycoprotein IIb/IIIa inhibitor, HbA1c = glycosylated hemoglobin, HRs = Hazard ratios, LVEDD = left ventricular end diastolic diameter, LVEF = left ventricular ejection fraction, LVEF = left ventricular ejection fraction, MACCEs = major adverse cardiovascular and cerebrovascular events, NGAL = Neutrophil gelatinase-associated lipocalin, non-IRA = non-infarct-related artery chronic total occlusion, NSTEMI = non-ST-segment elevation infarction, pPCI = primary percutaneous coronary intervention, ROC = receiver operating characteristic, TIMI = thrombolysis in myocardial infarction.

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1. Introduction

Multivessel coronary artery disease is common among patients with non-ST-segment elevation myocardial infarction (NSTEMI)[1] and their risk for major adverse cardiac events is varied. Patients with NSTEMI are a heterogeneous group with respect to the risk of having a major adverse cardiac event.[2] The presence of non-infarct-related artery chronic total occlusion (non-IRA CTO) in patients with NSTEMI further increases their risk of mortality at 12 months.[3] Several clinical, echocardiographic and biochemical factors influence the prognosis of NSTEMI in the follow-up period after pPCI. Novel, more reliable biomarkers are urgently needed to precisely identify those with high risk for adverse clinical outcomes following pPCI and to aid in the individualized prevention strategy formulation.

Neutrophil gelatinase-associated lipocalin (NGAL) is a 25-kDa protein associated with the endopeptidase matrix metalloproteinase-9. It is stored in granules of mature neutrophils and released by renal tubular cells in response to inflammation or ischemia.[4,5] Besides reflecting early tubular damage and acute kidney injury,[6–8] growing evidence of NGAL importance in atherosclerosis and myocardial remodeling.[9] In addition, NGAL is associated with the risk factors of atherosclerosis.[10] NGAL has also been considered as a strong prognostic factor of MACCEs in acute coronary syndrome patients.[11–13]

Approximately one-third of patients hospitalized for an acute myocardial infarction (AMI) have pre-existing diabetes mellitus (DM) due to the acute dysregulation of glucose metabolism during absolutely stress state.[14,15] Glycosylated hemoglobin (HbA1c) had been adopted as a reliable measure of chronic glycemia to help identifying DM, independent from serum glucose levels by the American Diabetes Association for almost one decade.[16] Elevated HbA1c is an important determinant of atherosclerosis beyond the risk associated with established diabetes.[17] The recognition of underlying DM during AMI by HbA1C could help earlier prevention and treatment of potential accompanying implications.[18]

There is limited evidence examining the involvement of NGAL and HbA1C in NSTEMI and single concomitant CTO. Our study aims to determine the ability of plasma NGAL and HbA1C levels to predict short-term and long-term major adverse cardiovascular and cerebrovascular events (MACCEs) in patients with NSTEMI and single concomitant CTO following successful pPCI. Furthermore, the layering research stratified by HbA1C is examined.

2. Methods

2.1. Patient and public involvement

A total 422 patients with NSTEMI and CTO were enrolled in the study upon admission to China–Japan Friendship Hospital, Beijing between January 2006 and April 2016 from 1864 NSTEMI patients in the same period. NSTEMI was diagnosed according to the criteria from European Society of Cardiology (ESC).[19] Exclusion criteria included: STEMI; rescue PCI, plans to undergo prior coronary artery bypass grafting; severe valvular and cardiomyopathy disease; no CTO or more than single CTO; left main disease; estimated life expectancy <12 months; severe renal insufficiency requiring dialysis; known contraindication to antiplatelet and anticoagulation therapy or contrast; and incomplete clinical data. Written informed consent was obtained, and the Ethics Committee/Institutional Review Board approval of China-Japan Friendship Hospital, Beijing has been obtained.

The following events were regarded as MACCEs in our study and recorded: revascularization; cardiogenic shock; ischemic stroke; cardiac death. After discharge, all patients underwent prospective and periodic follow-up by telephone interview and clinic referrals for 2 years until MACCEs were recorded, then the patient was removed from the study. A small number of patients suffered MACCEs during hospitalization. Patients were organized into MACCEs group and non-MACCEs group and independent predictors of poor prognosis were identified.

2.2. Therapy strategy

All patients were admitted to China–Japan Friendship Hospital, Beijing and received pPCI in the culprit vessel within 24 hours of presentation. All patients received standard oral dual antiplatelet therapy (aspirin 300 mg and clopidogrel 300 mg) as well as unfractionated heparin (initial 7000 to 10,000IU according to weight and boost as the operation progressed). Glycoprotein IIb/IIIa inhibitor (GPI, tirofiban), low molecular weight heparin, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, beta-blocker and statin were administered by the attending physician. Each patient underwent an echocardiograph within the first 3 days after admission. Medical history, laboratory results, and angiographic findings were collected and recorded in our database. The estimated glomerular filtration rate (eGFR) in our research was estimated using the simplified Modification of Diet in Renal Disease formula.[20] HbA1c was assessed on admission.

2.3. NGAL measurements

The evaluation of sNGAL (ng/ml) on admission and 7th day of hospitalization was performed via an enzyme-linked immunosorbent assay using the respective kits of R&D Systems according to the manufacturer's protocols, and the results were recorded using a flatbed reader (UNIPLAN; SPC PIKON, Russia). The reference range for sNGAL values was considered at 0.037 to 0.106 ng/mL.

2.4. Angiographic strategy

As long as one of the following criteria was present in a coronary artery, it could be regarded as the culprit vessel: definite or suspected thrombus; presence of thrombolysis in myocardial infarction (TIMI) flow grade <3; tight stenosis ≥70% consistent with noninvasive ischemia tests; or ruptured or ulcerated plaque. A CTO was defined as a non-IRA with 100% luminal narrowing before PCI and without anterograde flow or with anterograde or retrograde filling through collateral vessels. Given current practice guidelines for managing NSTEMI published by the ESC,[21] the culprit vessel was selected for PCI to decrease the rate of procedure complication and homogenize our research subjects.

2.5. Statistical analysis

Baseline characteristics of patients are expressed as mean ± standard deviation or median ± interquartile range for continuous variables and absolute figure (percentage) for categorical variables. Pearson X^2 was performed for between-group comparisons for qualitative variables and Student *t* or Mann–Whitney *U* test for continuous variables. Further, Cox proportional hazard regression model was performed to analyze the independent variables associated with the incidence of MACCEs. Variables selected for the multivariate Cox proportional hazard analysis were those with $P < .1$ in the univariate analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated by backwards stepwise regression analysis (Wald). The final follow-up was completed on April 20th, 2018. All statistical tests were 2-tailed and performed using SPSS 17.0 (SPSS, Inc, Chicago, IL); a *P* value $< .05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics of patients in individual groups

Of the 422 enrolled patients, 140 (33.2%) had MACCEs in the 2-year follow-up. 21 (5.0%) patients suffered cardiac death, while 55 (13.0%) received revascularization, 36 (8.5%) performed cardiogenic shock or decompensated heart failure, other 28 (6.6%) suffered new-onset or recurrence ischemic stroke. Among the MACCEs group, 19 (4.5%) patients reached end point during hospitalization. Twelve (2.8%) patients lost to follow-up after discharge (Fig. 1). Basic clinical characteristics, laboratory examinations, electrocardiograph results, angiographic and procedural characteristics are depicted in Table 1.

Significant differences were found between the 2 groups in age (61.6 ± 13.1 vs 58.8 ± 12.0, $P = .029$), neutrophil per cent (75.6 ± 12.4 vs 73.2 ± 11.4, $P = .030$), fasting blood glucose (FBG) (9.41 ± 2.76 vs 8.31 ± 2.77, $P = .001$), eGFR (89.5 ± 25.0 vs 96.3 ± 24.6, $P = .007$), left ventricular end diastolic diameter (LVEDD) (51.0 ± 5.9 vs 49.0 ± 5.9, $P = .002$) and left ventricular ejection fraction (LVEF) (45.7% ± 8.6% vs 49.2% ± 9.1%, $P < .001$). Consistent with the hypothesis, patients who suffered from MACCEs had higher NGAL on admission (1.91 ± 0.82 vs 1.71 ± 0.65, $P = .003$), NGAL at 7 days (2.70 ± 1.11 vs 2.21 ± 0.83, $P < .001$) and HbA1c (7.2% ± 1.9% vs 6.7% ± 1.7%, $P = .003$). Higher Killip classification was found more in the MACCEs group compared with survivals (32.1% vs 20.2%, $P = .007$). Differences in previous stroke rate (22.1% vs 15.2%, $P = .079$) and no-reflow onset during PCI (10.0% vs 5.3%, $P = .074$) was approaching significance between the 2 groups.

3.2. Multivariate logistic regression analysis of predictor of MACCEs

Through the multivariate cox regression analysis, when we enrolled NGAL on admission into the model, only LVEF (HR =

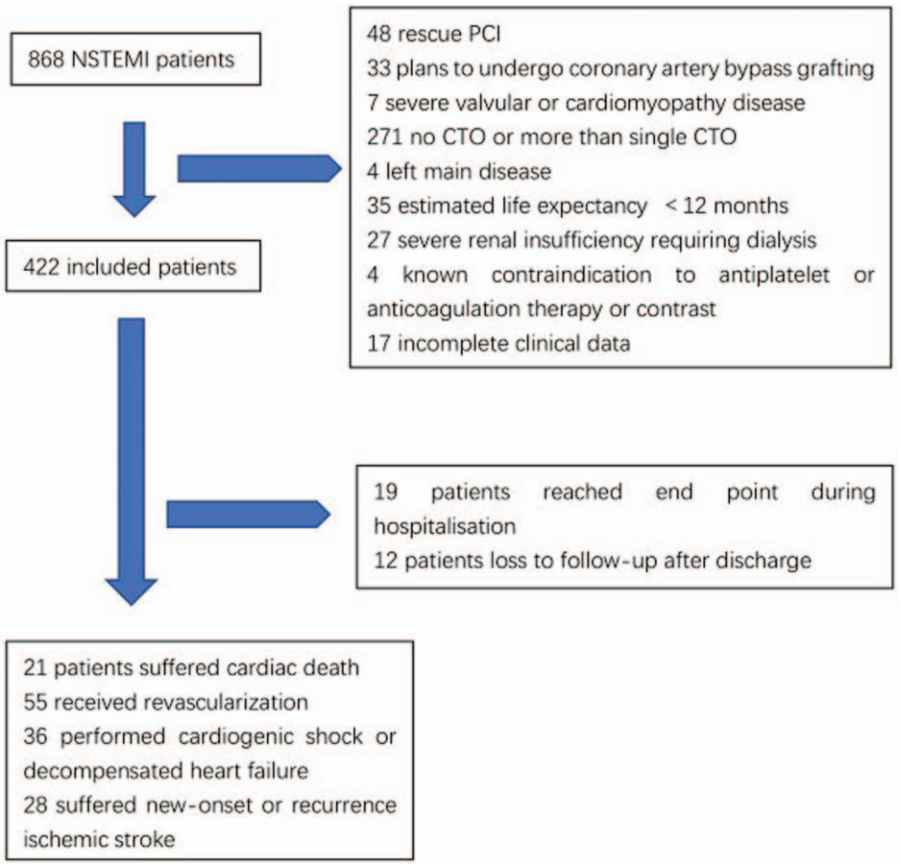

Figure 1. Patients selecting process and results reported. CTO = chronic total occlusion, NSTEMI = non-ST-segment elevation infarction, PCI = percutaneous coronary intervention.

Table 1

Basic clinical characteristics, laboratory examinations, electrocardiogram results, angiographic and procedural characteristic.

	MACCEs (N = 140)	Survivors (N = 282)	*P* value
Clinical characteristics			
Age, yr	61.6 ± 13.1	58.8 ± 12.0	.029*
Female, n (%)	38 (27.1)	71 (25.2)	.664
Heart rate, beats per min	82.1 ± 18.2	82.8 ± 19.9	.597
SBP, mm Hg	124.7 ± 32.0	125.3 ± 35.0	.982
Killip's classification>I, n (%)	45 (32.1)	57 (20.2)	.007*
DM, n (%)	104 (74.3)	191 (67.7)	.167
Hypertension, n (%)	60 (42.9)	142 (50.4)	.147
Previous stroke, n (%)	31 (22.1)	43 (15.2)	.079
Lab examination			
WBC $\times 10^9$/L	9.50 ± 3.18	9.79 ± 3.47	.500
Neutrophil (%)	75.6 ± 12.4	73.2 ± 11.4	.030*
Hemoglobin, g/L	137.1 ± 21.4	134.2 ± 23.3	.163
Platelet $\times 10^9$/L	246.4 ± 56.2	239.3 ± 58.1	.145
Albumin, g/L	37.2 ± 3.8	37.5 ± 4.3	.461
TC, mmol/L	6.67 ± 2.17	6.55 ± 2.17	.802
TG, mmol/L	1.55 ± 1.00	1.69 ± 0.976	.198
HDL-C, mmol/L	1.25 ± 0.42	1.19 ± 0.44	.149
LDL-C, mmol/L	3.89 ± 1.54	4.14 ± 1.57	.149
FBG, mmol/L	9.41 ± 2.76	8.37 ± 2.77	.001*
HbA1c (%)	7.2 ± 1.9	6.7 ± 1.7	.003*
NGAL at admission, ng/mL	1.91 ± 0.82	1.71 ± 0.65	.003*
NGAL 7 day, ng/mL	2.70 ± 1.11	2.21 ± 0.83	<.001*
BUN, mmol/L	6.60 ± 1.92	6.71 ± 2.11	.575
Creatinine, mmol/L	109.8 ± 53.5	99.1 ± 42.5	.172
Uric acid, mmol/L	315.9 ± 73.4	329.4 ± 77.6	.231
eGFR mL/min*1.73 m^2	89.5 ± 25.0	96.3 ± 24.6	.007*
D-Dimer, mg/L	1.1 (0.5–1.8)	1.1 (0.5–1.8)	.847
Peak CK-MB, U/L	63.9 (28.5–117.9)	52.7 (22.7–72.3)	.841
Peak cTnI, ng/mL	11.5 (5.5–18.2)	7.6 (2.4–10.8)	.385
Treatment			
ACEIs/ARBs, n (%)	85 (60.7)	184 (65.2)	.362
b-blocker, n (%)	80 (57.1)	171 (60.6)	.491
CCBs, n (%)	36 (25.7)	85 (30.1)	.344
Statins, n (%)	117 (83.6)	236 (84.3)	.851
Diuretics, n (%)	22 (15.7)	46 (16.3)	.875
Antiplatelet, n (%)	117 (83.6)	249 (88.3)	.178
GPI, n (%)	22 (15.7)	32 (11.3)	.206
Echocardiogram and electrocardiogram			
LADi, mm	36.6 ± 4.6	35.9 ± 5.3	.308
LVEDD, mm	51.0 ± 5.9	49.0 ± 5.9	.002*
LVEF, %	45.7 ± 8.6	49.2 ± 9.1	<.001*
Any ST depression, n (%)	25 (17.9)	62 (22.0)	.324
Culprit vessels, n (%)			
LAD	66 (47.1)	141 (50.0)	
LCX	19 (13.6)	56 (19.9)	.101
RCA	55 (39.3)	80 (30.1)	
Location of CTO, n (%)			
LAD	34 (24.3)	94 (33.3)	
LCX	42 (30.0)	76 (27.0)	.162
RCA	64 (45.7)	112 (39.7)	
Stent number	1.36 ± 0.50	1.35 ± 0.55	.684
Type B2/C lesion, n (%)	70 (50.0)	162 (57.4)	.148

Data are n/N (%) or mean ± standard deviation or median (25th to 75th percentile).

ACEIs = angiotensin-converting enzyme inhibitors, ARB = angiotensin receptor blockers, BUN = blood urea nitrogen, CCBs = calcium channel blockers, CK-MB = creatinine kinase MB, cTnI = cardiac Troponin I, CTO = chronic total occlusion, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, FBG = fasting blood glucose, GPI = glycoprotein IIb/IIIa inhibitor, HbA1c = glycosylated hemoglobin, HDL-C = high density lipoprotein, LAD = left anterior descending, LADi = left atrial diameter, LCX = left circumflex coronary artery, LDL-C = low-density lipoprotein, LVEDD = Left Ventricular End Diastolic Diameter, LVEF = left ventricular ejection fraction, MACCEs = major adverse cardiovascular and cerebrovascular events, NGAL = neutrophil gelatinase-associated lipocalin, PCI = percutaneous transluminal coronary intervention, RCA = right coronary artery, SBP = systolic blood pressure, TC = total cholesterol, TG = triglyeride, WBC = white blood cells.

* $P < .05$.

0.963, 95% CI 0.940 to 0.987, $P = .003$) and FBG (HR = 1.078, 95% CI 1.002 to 1.159, $P = .044$) were independent predictors of MACCEs of MACCEs within 2 years after pPCI. While we replace NGAL on admission by NGAL at 7 day, we found HbA1C (HR = 1.119, 95% CI 1.014 to 1.234, $P = .025$), LVEF (HR = 0.963, 95% CI 0.939 to 0.987, $P = .003$) and eGFR (HR = 1.020, 95% CI 1.006 to 1.035, $P = .006$) showed their predictive value for 2 years MACCEs, along with NGAL at 7 day (HR = 2.010, 95% CI 1.450 to 2.786, $P < .001$) (Table 2).

3.3. ROC analysis of predictor of MACCEs

ROC analysis failed to find the area under curve (AUC) of any indicator for 2-year MACCEs exceeding 0.7, although the *P* value for NGAL 7 day, HbA1C and LVEF alone was .0005, .0240 and .0021, respectively, while the AUC of NGAL at admission for 2-year MACCEs was 0.553 (95% CI 0.496 to 0.610, $P = .1443$). When only in-hospital MACCEs were observed, NGAL at admission >1.34ng/mL (AUC = 0.665, 95% CI 0.610 to 0.717, $P = .0103$), NGAL 7 day > 1.74ng/mL (AUC = 0.680, 95% CI 0.625 to 0.731, $P = .0054$) and LVEF ≤ 43.4% (AUC = 0.691, 95% CI 0.637 to 0.742, $P = .0298$) showed their predictive value. To sum up, NGAL 7 day and LVEF could predict both in-hospital and 2-year MACCEs, while higher NGAL at admission could only predict poorer in-hospital prognosis, HbA1C could merely be regarded as prognostic indicator for long-term follow up (Fig. 2, Table 3).

When patients were further subdivided according to HbA1C, 211 patients with HbA1C were over 6.5%. Among other patients with lower HbA1C, NGAL 7 day had a predictive advantage for MACCEs compared with HbA1C ($P = .043$), although no dominant advantage for predicting 2-year MACCEs was found between NGAL 7 day and NGAL at admission and LVEF. LVEF show its prognostic value in both groups ($P = .0327$ for HbA1C ≥ 6.5% and $P = .0246$ for HbA1C < 6.5%). Moreover, NGAL at admission was only predictive in patients whose HbA1C lower than 6.5% (AUC = 0.611, 95% CI 0.529 to 0.689, $P = .0468$, Table 4), in other words, among patients with HbA1C < 6.5%, NGAL, especially NGAL at 7 days during hospitalization, perform more ideal prognostic factor than HbA1C.

4. Discussion

The clinical outcomes in patients with NSTEMI and single concomitant CTO receiving pPCI are closely associated with the post-PCI NGAL concentration, particularly among those with relatively lower HbA1C. In addition, pre-PCI HbA1C and NGAL could also predict long-term and short-term prognosis respectively.

In patients with acute coronary syndromes, serum levels of NGAL could reflect the inflammatory status and the severity of coronary stenosis, which has high negative predictive value of clinical prognosis.[22] Patients with elevated levels of NGAL were found usually accompanied with slow coronary flow during coronary angiography.[23] Evidence regarding the association between increased NGAL and total mortality rates in elderly individuals has also been found.[24] The prognostic value of NGAL level at discharge, as an indicator to complement assessments of brain natriuretic peptide, is a strong prognostic indicator of 30 days outcomes in patients admitted for acute heart failure.[13] Barbarash et al[25] and Karetnikova et al[26] found measurement of NGAL level in patients with STEMI on the 12th to 14th day after hospital admission may improve prediction of

Table 2

Multivariate cox regression analysis for predictor of MACCEs.

Variables	Model with NGAL at admission			Model with NGAL 7 day		
	OR	95% CI	*P*	OR	95% CI	*P*
HbA1c	1.090	0.991–1.198	.076	1.119	1.014–1.234	.025*
FBG	1.078	1.002–1.159	.044*	1.064	0.987–1.147	.108
Neutrophil	1.018	1.000–1.038	.053	1.012	0.992–1.032	.257
eGFR	1.005	0.991–1.020	.475	1.020	1.006–1.035	.006*
Previous stroke	1.496	0.899–2.491	.121	1.431	0.857–2.388	.170
LVEF	0.963	0.940–0.987	.003*	0.963	0.939–0.987	.003*
LVEDD	1.031	0.997–1.067	.076	1.029	0.994–1.065	.101
Killip's classification>I	0.730	0.476–1.120	.150	0.698	0.455–1.071	.100
Age	1.008	0.991–1.024	.368	1.004	0.987–1.020	.661
NGAL at admission	1.442	0.907–2.290	.121	–	–	–
NGAL 7 day	–	–	–	2.010	1.450–2.786	<.001*

CI = confidence interval, eGFR = estimated glomerular filtration rate, FBG = fasting blood glucose, HbA1c = glycosylated hemoglobin, LVEDD = Left Ventricular End Diastolic Diameter, LVEF = left ventricular ejection fraction, MACCEs = major adverse cardiovascular and cerebrovascular events, NGAL = neutrophil gelatinase-associated lipocalin, OR = odds ratio.
* Statistically significant value ($P < .05$).

MI severity and adverse cardiovascular events. A study from Russia found NGAL level above 2.6 ng/mL on 12th day during hospital stay lead to 4 times all-cause mortality during 3-year follow-up.[27] Considering our mean length of stay (9.8 ± 3.6 days), we selected 7 days post pPCI as our second measuring time point. A similar study from Lindberg et al aiming at STEMI patients receiving PCI indicated higher NGAL is an independent predictor of an adverse cardiovascular outcome within 2 years of follow-up.[28] Adding NGAL into the Framingham risk score could both improves c-statistics of 10-year adverse outcome and correctly reclassifies participants into more accurate risk categories in the general population.[10] Combination of NGAL and TIMI score make a strong prognostic model for 1-year mortality rate in STEMI patients.[29]

NGAL is regarded taking part in the process of vascular remodeling. A complex of NGAL and MMP-9 located in atherosclerotic plaques to prevents degradation of MMP-9, the concentration of NGAL has been detected increased in plaques with intramural haematoma and central necrosis.[30] It is overexpressed in atheromatous plaques and correlates with features of plaque instability.[31] Animal experiment showed NGAL in the neutrophil secretome is a key inducer of macrophages with high capacity to engulf apoptotic cells, which mediate the post-myocardial infarction healing by polarizing macrophages towards a reparative phenotype.[32]

Besides the prognostic value of serum NGAL, urinary NGAL is also a sensitive prognostic Indicator. The level of urine NGAL is associated with NT-pro BNP concentration and play important role in predicting acute heart failure early after MI.[33] Urine NGAL was independently associated with future ischemic atherosclerotic events among patients with chronic kidney disease.[34]

El-sherbiny et al[35] found higher admission HbA1c level in AMI patients is associated with higher incidence of adverse cardiac events and lower rate of complete revascularization. Close association exist between HbA1c and degree of coronary lesion.[36] The potential explanation may be the sequential

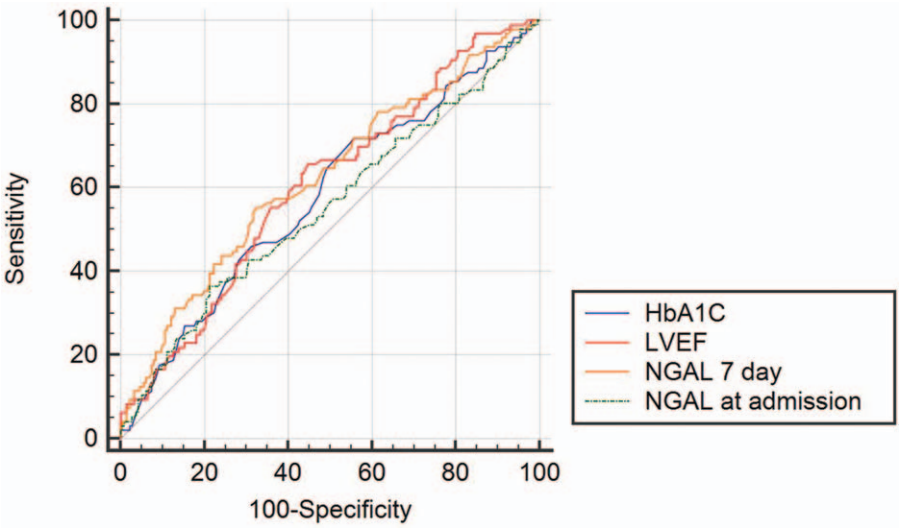

Figure 2. Receiver operating characteristic curve of LVEF, HbA1C, NGAL at admission and NGAL 7 day for predicting 2 years MACCEs after pPCI among patients with NSTEMI and single concomitant CTO. CTO = chronic total occlusion, HbA1c = glycosylated hemoglobin, LVEF = left ventricular ejection fraction, MACCEs = major adverse cardiovascular and cerebrovascular events, NGAL = neutrophil gelatinase-associated lipocalin, NSTEMI = non-ST-segment elevation infarction, pPCI = primary percutaneous coronary intervention.

Table 3

ROC analysis for in-hospital and 2-year MACCEs.

Parameters	AUC	95% CI	*P*	Threshold	Sensitivity, %	Specificity, %
2-yr MACCEs						
NGAL at admission	0.553	0.496–0.610	.1443	2.06	36.5	78.6
NGAL 7 day	0.622	0.566–0.677	.0005*	2.31	55.2	67.4
HbA1C	0.580	0.523–0.636	.0240*	5.8	71.9	44.2
LVEF	0.605	0.549–0.660	.0021*	47.8%	65.6	55.3
In-hospital MACCEs						
NGAL at admission	0.665	0.610–0.717	.0103*	1.34	71.4	71.0
NGAL 7 day	0.680	0.625–0.731	.0054*	1.74	71.4	73.4
HbA1C	0.520	0.463–0.577	.8125	4.1	35.7	83.8
LVEF	0.691	0.637–0.742	.0298*	43.4%	64.3	70.4

AUC = area under the curve, CI = confidence interval, HbA1c = glycosylated hemoglobin, LVEF = left ventricular ejection fraction, MACCEs = major adverse cardiovascular and cerebrovascular events, NGAL = neutrophil gelatinase-associated lipocalin, ROC = receiver operating characteristic.

* Statistically significant value ($P < .05$).

Table 4

ROC analysis for 2-year MACCEs among patients with separate level of HbA1C.

Parameters	AUC	95% CI	*P*	Threshold	Sensitivity, %	Specificity, %
HbA1C≥6.5% (n = 211)						
HbA1C	0.560	0.479–0.639	.2147	8.7	46.43	67.65
LVEF	0.601	0.521–0.678	.0327*	47.8	60.71	56.86
NGAL 7 day	0.574	0.493–0.653	.1241	2.31	51.79	66.67
NGAL at admission	0.503	0.423–0.583	.9502	1.78	39.29	67.65
HbA1C<6.5% (n = 211)						
HbA1C	0.541	0.459–0.622	.4682	5.8	32.50	84.07
LVEF	0.612	0.530–0.689	.0246*	47.8	72.50	53.98
NGAL 7 day	0.676	0.595–0.749	.0007*	2.63	50.00	79.65
NGAL at admission	0.611	0.529–0.689	.0468*	2.09	45.00	81.42

AUC = area under the curve, CI = confidence interval, HbA1c = glycosylated hemoglobin, LVEF = left ventricular ejection fraction, MACCEs = major adverse cardiovascular and cerebrovascular events, NGAL = neutrophil gelatinase-associated lipocalin, ROC = receiver operating characteristic.

* Statistically significant value ($P < .05$).

process participant by Advanced Glycation End Products: inflammation activation, atheroma formation, vascular stiffness modulation, and endothelial function disturbance by nitric oxide release reduction and vascular smooth muscle proliferation increase.[37]

A study focused on individuals aged 85 and older without diabetes mellitus showed higher HbA1c is associated with greater risk of MI, although not with stroke and mortality.[38] Another prior study found a greater risk of coronary heart disease with HbA1c levels exceeding 5.5% in both sex independent from the presence of DM.[39] Result from an earlier large study enrolling men and women without DM (mean age 38) indicated a significant higher mortality risk for individuals in the higher HbA1c categories.[40] A late recent meta-analysis pointed out elevated HbA1c level increased the risks of long-term mortality and reinfarction in nondiabetic patients with CAD.[41] Another meta-analysis demonstrated HbA1c level might be associated with higher risks of target vessel revascularization progression and nonfatal myocardial infarction among diabetic patients after PCI.[42] After liraglutide medication among patients with NSTEMI, HbA1c decrease was concomitant with left ventricular function improvement, reflected by the remarkable increase of LVEF, stroke volume and reduction of left ventricular end-systolic diameter and volume,[43] which could indirectly explain the relationship of HbA1C and clinical prognosis. One study similar with ours found HbA1c < 7.0 measured 2 years after PCI was associated with a reduced rate of MACCE.[44] Another research supported the predictive value of HbA1C for prognosis following the NSTEMI.[45]

We hypothesis the potential explanation of the subgroup analysis according to different HbA1C is that patients with relatively normal level of HbA1C fail to perform enough discrepancy to distinguish high-risk patients, to these patients, our novel index NGAL show its superiority in predicting MACCEs.

This study is not without limitations. Subject to the strict inclusion criteria, the study cohort was relatively small, which may affect the statistical results. A larger-scale study is warranted to further assess the risk of long-term MACCEs after pPCI in patients with NSTEMI and single concomitant CTO. The base level of NGAL prior to MI onset is difficult to obtain, therefore, the degree of NGAL increase is uncertain. Finally, urine NGAL concentration should be measured simultaneously if permitting.

5. Conclusion

In conclusion, NSTEMI and single concomitant CTO patients receiving pPCI with higher levels of NGAL during hospitalization are more likely to have poor in-hospital and 2-year prognosis after adjusting for other clinical parameters. Pre-PCI HbA1C and NGAL could also predict long-term and short-term prognosis respectively. Furthermore, NGAL 7 days may be beneficial in predicting MACCEs among those with HbA1C < 6.5%.

Author contributions

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