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Increased serum nardilysin is associated with worse long-term outcome of ST-elevation myocardial infarction

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Abstract. – OBJECTIVE: Nardilysin (N-arginine dibasic convertase, NRDC) is a kind of metalloendopeptidase associated with several inflammatory diseases. NRDC is reported to be eligible for early detection of acute coronary syndrome. However, the availability and effectiveness of NRDC in predicting the prognosis of patients with ST-elevation myocardial infarction has never been investigated.

PATIENTS AND METHODS: From January 2010 to January 2012, the prospective observational cohort study enrolled a total of 396 STEMI patients, who were sampled with blood within 24 hours after admission. A long-term follow-up was conducted to record the primary endpoint of all-cause mortality, as well as secondary endpoint of myocardial infarction, stroke, emergent revascularization and admission due to heart failure. Hazard ratio (HR) related to the serum NRDC level was estimated by Cox regression model.

RESULTS: The enrolled patients completed the follow-up with an average of 4.6 ± 0.5 years, of whom 24 patients died (primary endpoint, 6.1%), while 89 episodes of secondary endpoints occurred (22.5%). Patients with highest quartile level of NRDC (Q4 level, > 2041 pg/ml) were subjected to higher risk of all-cause death [HR 3.973, 95% CI (1.648-9.575), $p = 0.002$] compared to patients with lower three quartiles level of NRDC (Q1 to Q3, < 2041 pg/ml), while there was no difference in adverse events (p = 0.403).

CONCLUSIONS: The increased serum NRDC level at admission is associated with a higher risk of all-cause mortality for ST-elevation myocardial infarction patients.

Key Words:
Nardilysin, ST-elevation myocardial infarction, All-cause mortality, Adverse events, Acute coronary syndrome.

Introduction

ST-segment elevation myocardial infarction (STEMI) is the most serious type of acute coronary syndrome (ACS), which account for more than 30% of all death (the most common single death cause) and greatly increases the familial and social health burden[1]. Although the mortality of STEMI has declined continuously due to the development of novel biomarkers and revascularization, it remains a vital disease affecting the long-term survival of the patients[2]. The long-term prognosis of patients with STEMI is influenced by multiple factors[3,4], which are reported to be tested by some assessment tools such as SYNTAX score[5] and biomarkers[6,7]. However, these tools and biomarkers show some limitations of low accuracy, which necessitate novel biomarkers. Nardilysin, abbreviation of N-arginine dibasic convertase (NRDC), is a metalloendopeptidase of the M16 family binding HB-EGF, which functions to ectodomain shedding of multiple membrane proteins such as TNF-α, HB-EGF, NRG1[8]. Recently, NRDC has been reported to be valuable in early diagnosis of ACS[9]. Also, NRDC plays a role in the inflammation response[10], which is essential of myocardial infarction. We hypothesized that NRDC can be important in post myocardial infarction remodeling and associated with long-term prognosis, hence conducted the observational cohort study to investigate the potential of NRDC as a novel biomarker predicting the long-term outcome of patients with STEMI.

Patients and Methods

Patients

Patients admitted in the Department of Cardiology of our hospital meeting the following criteria would be enrolled in this study. Entry criteria: 1) be over 18 years old; 2) be diagnosed with

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STEMI; 3) receive revascularization treatment; 4) not die in the hospital due to STEMI; 5) be aware of the study and willing to participate. Exclusion criteria: (1) patients diagnosed with NSTEMI or unstable angina; (2) patients in coma or unconsciousness condition; (3) patients and family with poor communication ability or unwilling to cooperate with the follow-up. From January 2010 to January 2012, the prospective observational cohort study enrolled a total of 396 STEMI patients, who were sampled and given follow-up. All patients and their family were informed about this study and signed informed consent. This research was also approved by Medical Ethics Committee of First Affiliated Hospital, Xi'an Jiaotong University Health Science Center (Xi,an, China). All patients characteristic were collected from the electric database of the hospital. Routine myocardial injury markers including cTnT as well as CK-MB, and other laboratory indicators including Creatinine, NT-proBNP, hsCRP, were also tested.

NRDC Test

After the diagnosis, patient blood sample was acquired at a median of 24 hours after symptom onset and 18 hours after the PCI procedure, then the sample was centrifuged for 10 min at 2000 rpm. The serum was collected and stored in the -20°C refrigerator. Commercial NRDC ELISA kit (Human Nardilysin ELISA Kit, MyBioSource) was used to measure the serum NRDC level. According to the manufacture's instructing, the absorbance value was measured on a microplate reader set at a wavelength of 540 nm. Standard curve was plotted to get the absolute value of NRDC by comparing to the standard sample[11].

Diagnosis Standard

According to the 2017 ESC Guidelines for the Management of STEMI, STEMI was defined as electrocardiographic ST-segment elevation $\geq$ 2 mm in 2 or more contiguous chest leads or $\geq$ 1 mm in 2 or more limb leads or new onset of left bundle-branch block, together with chest pain or other typical symptoms and elevated troponin levels > 99th percentile[12].

Clinical Endpoint

Primary and secondary endpoint were studied as follows: primary endpoint was defined as all-cause mortality during the follow-up, while secondary endpoint was defined as a composite if adverse events including myocardial infarction, stroke, unscheduled revascularization, or rehospitalization for heart failure.

Follow-Up

The follow-up lasted from January 2010 to January 2017 by telephone or outpatient clinics. Every patient was given an annually inquiry of their conditions for about five years. Self-drop-out or miss contact was considered as censored data.

Statistical Analysis

In this study, IBM SPSS Statistics, version 19.0 (IBM, Armonk, NY, USA) was used for statistical analysis. Normality distribution test of the variables was conducted first to check the variables distribution condition. Continuous variables meeting the normal distribution were presented as mean ± standard deviations and categorical variables were presented as proportions, while continuous variables unfitting the normal distribution were described as median and interquartile range (IQR). Comparison of continuous variable of different groups was conducted with *t*-test of independent samples. Chi-square test was performed in different evaluations of categorical variables. Mann-Whitney test and Wilcoxon rank sum test were adopted for the comparison of different groups in non-normal variables of independent samples. As to the analysis of NRDC, it was divided into four quartiles according to the serum level, Q1, Q2, Q3, Q4, respectively. Cox hazard ratios (HR) model was adopted as the regression method to compare the relative hazard between patients with Q4 NRDC and patients with Q1-Q3 NRDC. Univariate analysis between covariates and endpoints was conducted, when covariates with p-value < 0.10 was entered into the multivariate analysis. Kaplan-Meier survivals curves and log rank tests were used to compare the survival status of patients in Q4 and Q1 to Q3. A p-value less than 0.05 was considered statistically significant.

Results

Patient Characteristics and Clinical Data

A total of 396 patients were enrolled in this research, of whom 350 patients completed full-term follow-up with a follow-up time of (48.0 ± 18.1) month. Among them, 24 patients (6.0%) died of all reasons, while 89 patients (22.5%)

Table I. Demographical characteristics and clinical data of the patients enrolled stratified by the endpoints.

Variables	Patients without endpoints (n = 283)	Patients with primary endpoint (n = 24)	Patients with secondary endpoint (n = 89)	*p*-value
Demographics				
Age (y, Mean ± SD)	62.4 ± 16.1	73.0 ± 11.2	66.3 ± 9.9	0.001
Gender (% male)	216 (76.3%)	21 (87.5%)	71 (79.8%)	0.394
BMI (kg/m^{-2})	24.9 ± 3.2	25.4 ± 2.8	23.9 ± 3.3	0.020
Smoking (%)	102 (36.0%)	4 (16.7%)	36 (40.4%)	0.097
NYHA			0.005	
I	73 (25.8%)	4 (16.7%)	20 (22.5%)	
II	90 (31.8%)	6 (25.0%)	32 (36.0%)	
III	99 (35.0%)	6 (25.0%)	25 (28.1%)	
IV	21 (7.4%)	8 (33.3%)	12 (13.5%)	
LVEF	49.5 ± 9.9	43.6 ± 12.6	48.7 ± 10.0	0.021
Comorbidities				
Heart failure	74 (26.1%)	11 (45.8%)	26 (29.2%)	0.115
Hypertension	67 (23.7%)	12 (50.0%)	28 (31.5%)	0.012
Diabetes mellitus	41 (14.5%)	4 (16.7%)	12 (13.5%)	0.922
Chronic kidney disease	14 (4.9%)	3 (12.5%)	4 (4.5%)	0.264
Chronic lung disease	37 (13.1%)	3 (12.5%)	5 (5.6%)0.152	
Cerebrovascular disease	18 (6.4%)	1 (4.2%)	5 (5.6%)0.893	
Tumor	7 (2.5%)	1 (4.2%)	3 (3.4%)0.825	
Laboratory test at admission				
Peak cTnT (ng/dL)	4.86 (3.11-6.46)	6.24 (3.82-6.95)	4.07 (2.56-6.02)	0.031
Peak CK-MB (ng/dL)	557.8 (421.0-673.2)	468.7 (421-673)	588.0 (406.7-713.1)	0.368
Creatinine (umol/L)	104.0 (75.0-133.0)	107.0 (78.8-136.0)	89.0(69.5-126.0)	0.146
NT-proBNP (ng/L)	69.6(27.0-122.9)	107.2(58.3-180.5)	77.2(41.8-133.5)	0.070
hsCRP (mg/L)	21.6(12.9-29.7)	30.2 (22.0-41.3)	26.2(17.6-35.2)	< 0.001

Abbreviations: BMI, body mass index; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

developed adverse events. We compared the demographical characteristics and clinical data of patients with different endpoints (Table I). Patients in primary endpoint had significantly higher age, BMI, NYHA level and proportion of hypertension (all $p < 0.05$). As for laboratory test, there was no difference between all types of patients in CK-MB, Creatinine and NT-proBNP at admission (all $p > 0.05$), while cTnT and hsCRP were significantly higher in patients with primary endpoint ($p < 0.05$). Demonstrated in Figure 1, NRDC of patients with primary endpoint was (2058 IQR (1614-2827)) pg/ml, which was significantly higher than patients with secondary endpoint (1468(850-2080) pg/ml) and patients without endpoint (1321(741-2002) pg/ml) ($p < 0.001$), while NRDC between patients with secondary endpoint and patients without endpoint didn't differ significantly ($p = 0.154$).

Primary Endpoint

The univariate Cox hazard regression analysis showed that age, NYHA level, LVEF, hypertension, NT-proBNP and hsCRP was associated with primary endpoint, which were used to adjust the HR in multivariate Cox hazard regression analysis (Table II). Hazard ratio (HR) results of patients with Q4 level of NRDC compared with Q1 to Q3 level of NRDC was showed in Table III. Patients with Q4 level of NRDC had a 3.973 95% CI (1.648-9.575) time hazard of dying compared to those with Q1-Q3 level of NRDC, which was adjusted by covari-

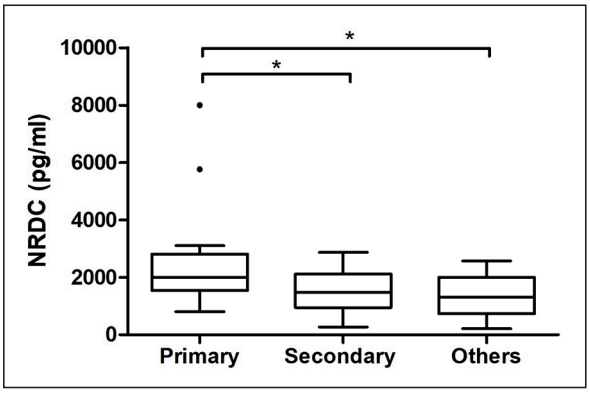

Figure 1. Serum NRDC level of patients with different endpoints. *$p < 0.05$.

Table II. Univariate Cox regression analysis between covariates and primary endpoint (Q4 vs. Q1 to Q3).

Covariates	HR	95% CI	*p*-value
Age	1.058	1.016-1.081	0.003
Gender (male to female)	2.121	0.632-7.110	0.223
BMI	1.071	0.943-1.216	0.289
Smoking	2.890	0.988-8.457	0.053
NYHA	1.668	1.082-2.571	0.021
LVEF	0.949	0.912-0.987	0.009
Heart failure	2.142	0.959-4.781	0.063
Hypertension	2.866	1.287-6.380	0.010
Diabetes mellitus	1.212	0.414-3.546	0.726
Chronic kidney disease	2.500	0.746-8.384	0.138
Chronic lung disease	1.067	0.318-3.578	0.916
Cerebrovascular disease	0.637	0.086-4.717	0.659
Tumor	1.508	0.204-11.165	0.688
Peak cTnT	1.193	0.967-1.472	0.100
Peak CK-MB	0.998	0.995-1.001	0.217
Creatinine	1.002	0.999-1.004	0.131
NT-proBNP	1.002	1.000-1.003	0.046
hsCRP	1.068	1.024-1.113	0.002

Abbreviations: BMI, body mass index; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

ates of age, smoking, NYHA, Hypertension, NT-proBNP and hs-CRP. Kaplan-Meier curve of Figure 2 demonstrated a significant difference of survival rates between patients with Q4 level of NRDC and those with Q1-Q3 level of NRDC ($p = 0.006$).

Secondary Endpoint

There was no significant difference between patients with Q4 level of NRDC compared with Q1 to Q3 level of NRDC in developing composite of adverse events ($p = 0.403$), as well as individual adverse events (all $p > 0.05$) (Table III). Also, there was no disparity in survival between those two kinds of patients ($p = 0.873$) (Figure 3).

Discussion

By continuous 5 years' follow-up, this research demonstrated that serum NRDC at admission of patients died during the follow-up was significantly higher than those who survived, while serum NRDC of patients with adverse events was close to those without any. Patients with highest quartile of serum NRDC were at about 3.973 times risk dying after the STEMI, while the risk of developing adverse events including heart failure, stroke, revascularization, recurrent myocardial infarction wasn't increased when compared with those with lower three quartiles. This study has advantages of relatively large sample size, strictly planned design, well-performed follow-up and meaningful results, which

Table III. Hazard Ratio (HR) of endpoint for patients with Q4 level of NRDC compared with Q1 to Q3 level of NRDC.

	Unadjusted HR (95% CI)	*p*-value	Adjusted* HR (95% CI)	*p*-value
Primary endpoint	2.938 (1.320-6.541)	0.008	3.973 (1.648-9.575)	0.002
Secondary endpoint				
Myocardial infarction	1.414 (0.763-2.619)	0.271	1.307 (0.698-2.449)	0.403
Stroke	0.727 (0.081-6.509)	0.776	0.659 (0.068-6.428)	0.720
Emergent revascularization	1.294 (0.563-2.976)	0.544	1.413 (0.595-3.353)	0.433
Readmission due to heart failure	0.031 (0.000-7.835)	0.219	0.025 (0.000-19.876)	0.960
Overall	1.039 (0.651-1.659)	0.873	0.970 (0.600-1.568)	0.901

*HR adjusted by covariates of Age, smoking, NYHA, Hypertension, NT-proBNP and hs-CRP.

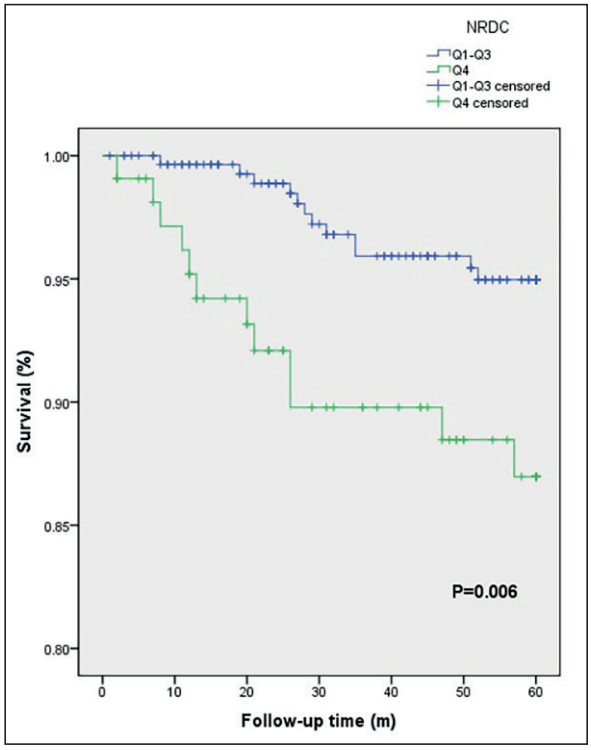

Figure 2. Survival curves of the primary endpoint for the patients with highest Q4 level NRDC and patients with Q1-Q3 level NRDC. Log rank test was used for the comparison.

make the conclusions valid and persuasive. In physiological conditions, NRDC functions as a metalloprotease that cleaves peptides, such as dynorphin-A, alpha-neoendorphin, and glucagon, at the N-terminus of arginine and lysine residues in dibasic moieties[13]. NRDC plays a role in the process of inflammation, metaplasia, and tumors[14]. Most of NRDC studies focus on diabetes[15], liver fibrosis[16], and autoimmune arthritis[17]. However, Chen et al[9] provided a clue that NRDC is promising in early diagnosis of ACS on the basis of the participation of NRDC in the process of MI which is independent of cell necrosis. As previously proved, we supposed that NRDC plays a role in the inflammation process after myocardial infarction, when NRDC is secreted increasingly from cardiomyocytes in response to myocardial ischemia. As a result, NRDC might increase sharply when there was serious inflammation response in the myocardium, which made NRDC a possible biomarker to predict the prognosis of the patient. The results of this research supported the hypothesis, which demonstrated that higher serum was associated with worse prognosis. Multiple tools have been developed to evaluate the condition of the STEMI patients and used to predict the long-term prognosis. Tarasov et al[5] evaluated the prognostic value of SYNTAX score in patients with STEMI undergoing PCI, which showed that patients with a SYNTAX score over 23 points have a higher rate of the combined endpoint of death, myocardial infarction, and target vessel revascularization (OR 2.8) as compared with patients with a lower SYNTAX score. SYNTAX score system is a unique tool to score complexity of coronary artery disease, which consists of the lesion information of coronary artery and demographical characteristics. We also found the difference between patients with/without primary endpoint in age, BMI, LVEF, hypertension and some laboratory test results, which correlated well with the SYNTAX score system. Other biomarkers have also been explored before to evaluate their value in assessing the long-term risk. He et al[18] reported that Neutrophil-to-lymphocyte ratio (NLR) was a useful and powerful predictor of mortality and adverse-outcomes in Chinese patients presenting with STEMI. Ritschel et al[19] showed a strong

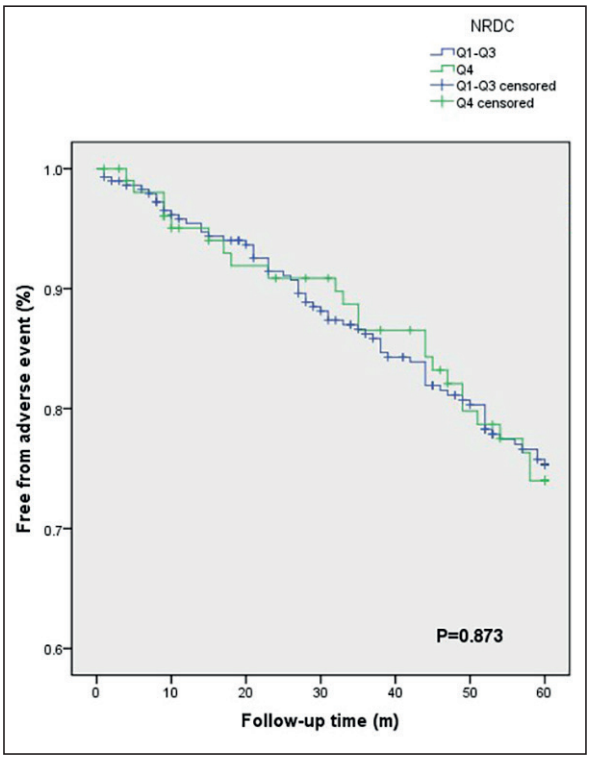

Figure 3. Survival curves of the secondary endpoint for the patients with highest Q4 level NRDC and patients with Q1-Q3 level NRDC. Log rank test was used for the comparison.

association between circulating levels of IL-6 receptor and gp130 and long-term clinical outcomes in STEMI. Compared with studies above, the study we conducted divided the outcome into primary endpoint and secondary endpoint rather than a composite combined all adverse events together, which helps to illustrate the specific relationship more accurately. A paradoxical finding of this study is the statistical insignificance of serum NRDC level and secondary endpoint, which seems to contradict our hypothesis. Supposedly, NRDC should be associated with the adverse events after STEMI since it participates in the restoring process. However, we didn't find any difference between patients with Q4 level NRDC and Q1-Q3 level NRDC in the risk of composite or individual adverse event. We suggest that the paradox can be explained by two reasonable speculations. First, the sample size may not be enough to examine the difference, even individual adverse event such as heart failure. Second, the serum NRDC level only differs in severe lethal conditions rather than mild ones leading to some moderate complications. Implications of this study exist in both experimental and clinical settings. On one hand, it provides more clues that NRDC plays some role in cardiovascular system, especially in coronary artery disease. On the other hand, NRDC examination can be a promising evaluation for predicting the long-term prognosis and guide the follow-up in its own manner or combined with other indications. Nevertheless, some limitations of this study must be noted. First, the conclusion needs to be consolidated in a more large-scale cohort, especially the association between NRDC level and adverse events. Second, the sample time of this study was within a period of time rather than fixed time, which might affect the serum level and the final results. Last, although some clinical factors had been included in the Cox regression model to adjust the HR value, other confounding factors might be neglected, such as lesion type, time from STEMI to revascularization.

Conclusions

By observing the long-term clinical outcomes of patients with STEMI stratified by serum NRDC level, we demonstrated that patients with higher NRDC level at admission are at higher risk of dying after the STEMI, with similar risk of developing adverse events. Future investigations should focus on the fundamental mechanism between NRDC and myocardial infarction. Also, a larger cohort study is expected to validate and promote the conclusions.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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