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Prognostic value of fractalkine/CX3CL1 concentration in patients with acute myocardial infarction treated with primary percutaneous coronary intervention

Xu Bing[a,1], Qian Yanxia[b,1], Zhao Yingming[b], Fang Zhen[a], Tang Kangting[b], Zhou Ningtian[b], Li Dianfu[b,*], Wang Junhong[b,c,*]

[a] Department of Cardiology, Northern Jiangsu Province Hospital and Clinical Medical College, Yangzhou University, Yangzhou, China
[b] Department of Cardiology, The First Affiliated Hospital with Nanjing Medical University, Nanjing, China
[c] Department of Cardiology, The People's Hospital of Kizilsu Kirghiz Autonomous Prefecture, Xinjiang, China

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ABSTRACT

Background: Recent studies demonstrated that fractalkine (FKN) is critically involved in the regulation of inflammation and cardiac function.

Objective: This study aimed to investigate the prognostic value of circulating FKN in patients with ST-elevated acute myocardial infarction (STEMI) after primary PCI.

Methods: We enrolled ninety consecutive STEMI patients and investigated the association of circulating FKN with myocardial salvage and the occurrence of major adverse cardiac events (MACE) after PCI.

Results: During a median follow-up of 387 days, total 15 MACE (16.67%) were registered in the study population. Patients with MACE were more likely to be occurred in elderly patients with 3-vessel disease. Correlation analysis demonstrated the level of FKN at day 1 after PCI (FKN@day-1) not only significantly correlated with the levels of hs-TnT at day 7 after PCI ($R^2 = 0.06$; $p = 0.02$) but inversely correlated with the measurements of LVEF at 1-month observation ($R^2 = 0.10$; $p = 0.00$). Kaplan-Meier survival analyses further revealed that patients with the level of FKN@day-1 above the median had a higher incidence of MACE compared with those whose FKN@day-1 levels below the median (log-rank test $x^2 = 13.29$, $p < 0.001$). In addition, multivariate Cox regression analysis demonstrated that FKN@day-1 was an independent predictor of MACE (hazard ratio: 4.63; 95% confidence interval: 1.53–14.01; $p = 0.00$), together with WBC count and 3-vessel disease for STEMI patients.

Conclusions: Our study demonstrates that FKN@day-1 is negative correlated with myocardial salvage after acute myocardial infarction and might be a valuable prognostic marker of MACE in patients with STEMI undergone PCI.

1. Introduction

Although the mechanisms leading to myocardial injury and repairment after acute myocardial infarction (AMI) remain incompletely understood, research has shown that inflammation and immune cells paly a key role in this pathophysiological process [1–6]. Of which the chemokine family is particularly important and of interest [1,5,7]. It has been reported that chemokines can regulate the infiltration of inflammatory cells, including T cells, B cells, monocytes/macrophages, and dendritic cells to the injury sites right after the onset of AMI [8]. Chemokines also a strong inducer for the proliferation of T cells and B cells, as well as promoting the production mass of cytokines and other chemokines to amplify the inflammation, aggravate the tissue damage or even enhance angiogenesis [1,9–11]. Therefore, chemokines may be important players in the pathogenesis of AMI, and blocking the certain actions of chemokines could be a novel approach for reverse the pathological remodeling after AMI.

Fractalkine/CX3CL1 (FKN) is a recently discovered chemokine. It has two forms: the membrane-anchored and the free soluble form (sFKN). The membrane-anchored FKN is expressed primarily on the surface of activated endothelial, smooth muscle cells, anchoring the circulating monocytes and T cells to the injury site [12]. Meanwhile,

* Corresponding authors at: Department of Cardiology, The First Affiliated Hospital of Naning Medical University, Guangzhou Road 300, Nanjing 210029, China.
E-mail addresses: lidianfu@jsph.org.cn (D. Li), wangjunhong@jsph.org.cn (J. Wang).
[1] These authors contributed equally to this work.

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the sFKN act as a chemotactic stimulus, which strongly induces the production of inflammation cells [13,14]. Studies have shown that the level of sFKN is increased in unstable coronary artery disease, and may be related to plaque rupture [14–16]. In addition, it has been shown that both myocardial and soluble FKN are increased in heart failure and could be a valuable prognostic biomarker for chronic heart failure [17,18]. Although sFKN is reported to involve in myocardial ischemia/reperfusion injury of AMI patients and can be a risk factor for cardiovascular disease (CVD) [19], little is known about the relationship between the sFKN and the subsequent cardiac function and outcomes in AMI patients.

In the present study, we aimed to investigate the levels of sFKN and evaluate its prognostic values in AMI patients who underwent primary percutaneous coronary intervention (pPCI).

2. Patients population

The study protocol had been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments and was approved by the institutional ethics committee of Northern Jiangsu province hospital and clinical medical college of Yangzhou University (2016KY-186). The informed consent was obtained from either the patients or their family members. We recruited ninety consecutive STEMI patients admitted to the hospital between September 2016 and April 2017 meeting the study criteria. STEMI was diagnosed if a patient presenting with ischemic symptoms and persistent ST-segment elevation on the electrocardiogram (ECG) with the following criteria: typical rise in biomarkers of myocardial necrosis or progress to Q-wave myocardial infarction [20]. All enrolled patients received immediate PCI without previous fibrinolysis. Patients who naive to anti-platelets were treated with 300 mg aspirin and 180 mg Ticagrelor in the ambulance or the emergency department. If the patients were taking aspirin for a long-term, no loading dose was needed; the same was true for Ticagrelor. Exclusion criteria were prior myocardial infarction (MI) or history of coronary artery bypass graft surgery (CABG), cardiogenic shock, time to pPCI > 24 h, atrial fibrillation, Killip class > III, end-stage renal disease (glomerular filtration < 30 mL/min) or known malignancy. Patients with those factors which may affect inflammatory status, such as infectious disease, inflammatory disorders or receiving treatments including steroids and non-steroidal anti-inflammatory drugs were also excluded from this study.

2.1. Collection of clinical and biochemical data

Demographic, and clinical data of those patients were obtained during hospitalization. All laboratory biochemical data were obtained from the samples of the first 12–24 h after PCI unless specifically indicated. Standard laboratory tests were performed to measure the serial high-sensitivity troponin T measurements (hs-TnT, Roche Diagnostics, USA). Serial FKN was measured by commercial kits (Luminex Screening Human Magnetic Assay, LXSAHM-03, R&D company, USA) at Day-0 (on admission) and day-1 (first 12–24 h after pPCI) samples. Peripheral venous blood was collected, centrifuged, and the serum was stored at -70 °C for batched analysis. All study patients received standard treatment according to current guidelines [20].

2.2. Invasive coronary angiography

Coronary angiography (CA) was performed by using Seldinger technique via puncture of the femoral or radial artery. Immediately after CA, all enrolled patients received immediate PCI according to CA results. The type of stent and its diameter and length were selected on the basis of angiographic measurements.

2.3. Transthoracic echocardiography

Transthoracic echocardiography (TTE) was performed in the first day (day-1) after pPCI, and 1-month after discharge using a GE Vivid 7 ultrasound system system in the standard parasternal and apical views. Left ventricular ejection fraction (LVEF) was calculated by using Simpson's method. Left ventricular dysfunction was defined as LVEF < 55%. Two experienced cardiologists assessed images independently, unaware of the patients' other clinical data.

2.4. Follow-up study and outcome measurements

Patients were observed with a median follow-up of 387 days after enrollment in the study. Follow-up information was gathered by clinical visits or telephone contacts. One visits were scheduled in the out-patient department at 1 month for echocardiographic data after AMI. The clinical outcome was defined as the occurrence of a composite MACE during follow-up, which including all-cause mortality, rehospitalization due to heart failure (HF), recurrent AMI or stroke/transient ischemic attack. Specifically, when 2 MACEs occurred in 1 patient (eg, recurrent AMI and death in the follow-up), only 1 cumulative MACE will be documented. Two cardiologists performed all follow-up independently and were blinded to the results while taking the clinical follow-up work.

2.5. Statistical analysis

Categorical variables were presented as counts (percentages), whereas continuous variables were reported as mean ± SD or median with IQR (Q1–Q3) depending on their distribution. Kolmogorov–Smirnov test was used to verify the assumption of normality. Categorical variables were compared between MACE (+) and MACE (−) patients by using χ^2 test or Fisher's exact test, and continuous variables were compared by using Student t test or Mann–Whitney U test as appropriate. Correlations between variables were analyzed by using Pearson's or Spearman's rank correlation according to the data distribution.

The diagnostic performance of FKN for the prediction of cumulative MACE was evaluated by using receiver operating characteristic curve (ROC) analysis, and the optimal threshold was based on the point of combined best sensitivity/specificity results.

Moreover, the association between FKN and cumulative MACE events after PCI was evaluated as a Hazard ratio (HR) and corresponding 95% confidence interval (CI) with the use of multivariable Cox regression analysis. Finally, Kaplan-Meier survival analysis was conducted to compare the difference in survival rate between patients with high and low levels of FKN using the log-rank (Mantel-Cox) test. All statistical analyses were performed by using SPSS20.0 software (SPSS Inc. USA) or GraphPad Prism 6.0e (GraphPad Software Inc. USA) as appropriately. P-values < 0.05 were considered statistically significant.

3. Results

3.1. Patient characteristics

Characteristics of the study population are shown in Table 1. Ninety STEMI patients (70 men, 77.78%) on hospital admission were eligible for this study. Mean age of the patients was 63.93 ± 11.94 years. The symptom-to-balloon time (time from symptom onset to receiving balloon dilation treatment) was 7.36 ± 5.69 h. On admission, all patients had elevated hs-TnT (normal upper limitation, 0.014 μg/L). The patients were then divided into 2 groups according to the occurrence of MACE events or not during follow-up. No significant difference was observed in sex, BMI, medical treatment after hospitalization, history of hypertension, diabetes mellitus, dyslipidemia or time from symptom onset to receiving balloon dilation treatment between the patients with

Table 1
Baseline characteristics and comparison between the patients with and without MACE events occurrence.

Characteristic	MACE (+) (n = 15)	MACE (−) (n = 75)	p value
Demographic characteristics			
Age (years)	71.33 ± 10.46	62.45 ± 11.17	0.01
Male gender, n (%)	9 (60.00%)	61 (81.33%)	0.07
Hypertension, n (%)	11 (73.33%)	45 (60.00%)	0.33
Diabetes mellitus, n (%)	5 (33.33%)	17 (22.67%)	0.38
Dyslipidemia, n (%)	6 (40.00%)	34 (45.33%)	0.70
Current smoker, n (%)	5 (33.33%)	40 (53.33%)	0.16
BMI (kg/m^2)	24.13 ± 3.85	24.26 ± 2.29	0.87
Symptom-to-balloon time, (h)	6.87 ± 3.68	7.43 ± 6.03	0.71
Medical treatment			
Statin, n (%)	14 (93.33%)	74 (98.67%)	1.00
Beta-blocker, n (%)	14 (93.33%)	60 (80.00%)	0.22
ACEI/ARB, n (%)	8 (53.33%)	42 (56.00%)	0.85
DAPT, n (%)	15 (100.00%)	75 (100.00%)	1.00
Nitroglycerin, n (%)	11 (73.33%)	42 (56.00%)	0.22
CA results			
1-vessel disease, n (%)	2 (13.33%)	35 (46.67%)	0.02
2-vessel disease, n (%)	2 (13.33%)	14 (18.67%)	0.62
3-vessel disease, n (%)	11 (73.33%)	26 (34.67%)	0.05
Culprit lesion			
LAD, n (%)	12 (80.00%)	39 (52.00%)	0.05
LCX, n (%)	1 (6.67%)	13 (17.33%)	0.45
RCA, n (%)	2 (13.33%)	23 (30.67%)	0.21
Stent numbers	1.33 ± 0.49	1.15 ± 0.43	0.14

MACE: Major adverse cardiac event; BMI: Body mass index; Symptom-to-balloon time: time from the onset of chest pain to receiving balloon dilation treatment; DAPT: double anti-platelet treatment; CA: conroary angiography; LAD: left anterior descending artery; LCX, left circumflex artery; RCA: right coronary artery.

or without MACE occurrence. However, coronary angiographic results demonstrated that more 3-vessel CAD patients were seen in MACE (+) group than those patients with no MACE occurred (73.33% vs. 34.67%, p = 0.05) during follow-up. In addition, the patients with MACE occurred had significantly higher level of WBC count, hs-cTnT at day-7 (cTnT@day-7), and lower LVEF at 1 month (LVEF@1-month) than those patients without MACE events (Table 2).

3.2. The dynamic changes of serum FKN concentration in STEMI patients

On admission, the blood was sampled, and the circulating FKN was measured. After 12–24 h of PCI, a decreased but not statistically significant level of FKN was observed when compared with the admission samples (777.00 (600.29–1148.00) vs. 848.71 (724.27–1261.50), $p > 0.05$). However, the levels of serum FKN@day-1 were significantly higher in MACE (+) patients than those in MACE (−) patients (1625.21 (1075.47–1929.03) vs. 731.52 (583.29–986.38), $p < 0.01$). In contrast, no significant difference level of FKN was observed in the admission samples between the two group of patients (Table 2).

3.3. The concentration of circulating FKN correlates with the myocardial injury and cardiac function

Both level of Pre-PCI (on admission) and Post-PCI FKN@day-1 significantly correlated with the levels of cardiac damage biomarker (hs-TnT at day 7 after PCI ($R^2 = 0.05$; $p = 0.03$ for pre-PCI & $R^2 = 0.06$; $p = 0.02$ for Post- PCI) (Fig. 1A and B). Furthermore, the concentration of FKN@day-1 inversely correlated with the measurements of LVEF at 1-month observation ($R^2 = 0.10$; $p = 0.00$) (Fig. 1C). However, no correlation was found between the DELTA FKN (FNK@day 0- FKN@day 1) and those biomarkers such as TnT@day 7 ($R^2 = 0.005$, $p = 0.53$) or CRP@day 7 ($R^2 = 0.003$, $p = 0.70$). In addition, patients with impaired LVEF (< 55%) at 1-month were found to have the higher levels of FKN@day-1 compared with those patients with normal LVEF (Fig. 1D). Meanwhile, the FKN levels measured on admission did not correlate with LVEF.

3.4. FKN predicts cardiac outcome after primary PCI in STEMI patients

The median length follow-up day of the STEMI patients was 387 days (range, 1–485 days). During the follow-up period, 15 patients occurred MACE events, of which, 8 patients died, 5 readmitted with HF, and 2 experienced recurrent AMI. No patient was lost to follow-up. Kaplan-Meier survival analysis demonstrated that higher FKN@day-1 (> median) was a useful predictor of MACE in patients with STEMI. Fig. 2 demonstrated that patients below the median levels of FKN@day-1 had a significantly lower incidence of MACE (log-rank test $x^2 = 13.29$, $p < 0.001$) compared with those above the median.

Table 2
Clinical parameters characteristic of the study group.

Characteristic	Overall (n = 90)	MACE (+) (n = 15)	MACE (-) (n = 75)	p value
Laboratory parameters				
hs-TnT@day-0, ug/L	7.50 ± 9.30	8.28 ± 10.00	7.35 ± 9.22	0.72
hs-TnT@day-3, μg/L	13.73 ± 9.07	14.80 ± 9.82	13.54 ± 9.00	0.65
hs-TnT@day-7, μg/L	5.62 ± 5.90	10.46 ± 6.80	4.90 ± 5.41	0.00
hs-CRP@day-1, mg/L	5.64 (2.78–17.75)	10.5 (4.75–28.63)	5.64 (2.77–16.23)	0.37
hs-CRP@day-7, mg/L	5.19 (2.46–8.48)	7.63 (4.01–22.39)	4.58 (2.45–8.44)	0.24
WBC, $\times 10^9$/L	9.91 ± 3.26	12.24 ± 3.93	9.48 ± 2.95	0.00
Neutrophils, (%)	73.66 ± 13.70	75.06 ± 20.03	73.40 ± 12.33	0.68
Monocyte, (%)	6.22 ± 3.62	7.84 ± 7.46	5.92 ± 2.28	0.07
TC, mmol/L	4.55 ± 1.13	4.62 ± 1.60	4.53 ± 1.04	0.81
TG, mmol/L	1.51 ± 0.88	1.37 ± 0.66	1.54 ± 0.92	0.54
LDL-C, mmol/L	2.69 ± 0.90	2.78 ± 1.17	2.68 ± 0.86	0.70
HDL-C, mmol/L	1.11 ± 0.31	1.17 ± 0.36	1.10 ± 0.31	0.49
Glucose, mmol/l	7.53 ± 3.96	8.14 ± 5.21	7.41 ± 3.72	0.54
Creatinine, μmol/L	79.21 ± 31.26	85.00 ± 38.48	78.05 ± 29.78	0.44
FKN@day-0 (pg/mL)	848.71 (724.29–1261.50)	927.41 (879.00–1743.00)	819.15 (702.83–1153.00)	0.06
FKN@day-1 (pg/mL)	777.00 (600.29–1148.00)	1625.21 (1075.47–1929.03)	731.52 (583.29–986.38)	0.00
Echocardiological parameters				
LVEF@day-1 (%)	0.46 ± 0.08	0.44 ± 0.08	0.47 ± 0.09	0.23
LVEF@1-month (%)	0.52 ± 0.09	0.47 ± 0.08	0.53 ± 0.09	0.03
Stent numbers	1.13 ± 0.53	1.25 ± 0.62	1.10 ± 0.51	0.37

Hs-TnT: high sensitivity troponin T; Hs-CRP: high sensitivity C-reactive protein; WBC: white blood cell; TC: total cholesterol; TG: triglyceride; LDL-C: low density lipoprotein; HDL-C: high density lipodensity; FKN: fractalkine; LVEF: left ventricular ejection fraction.

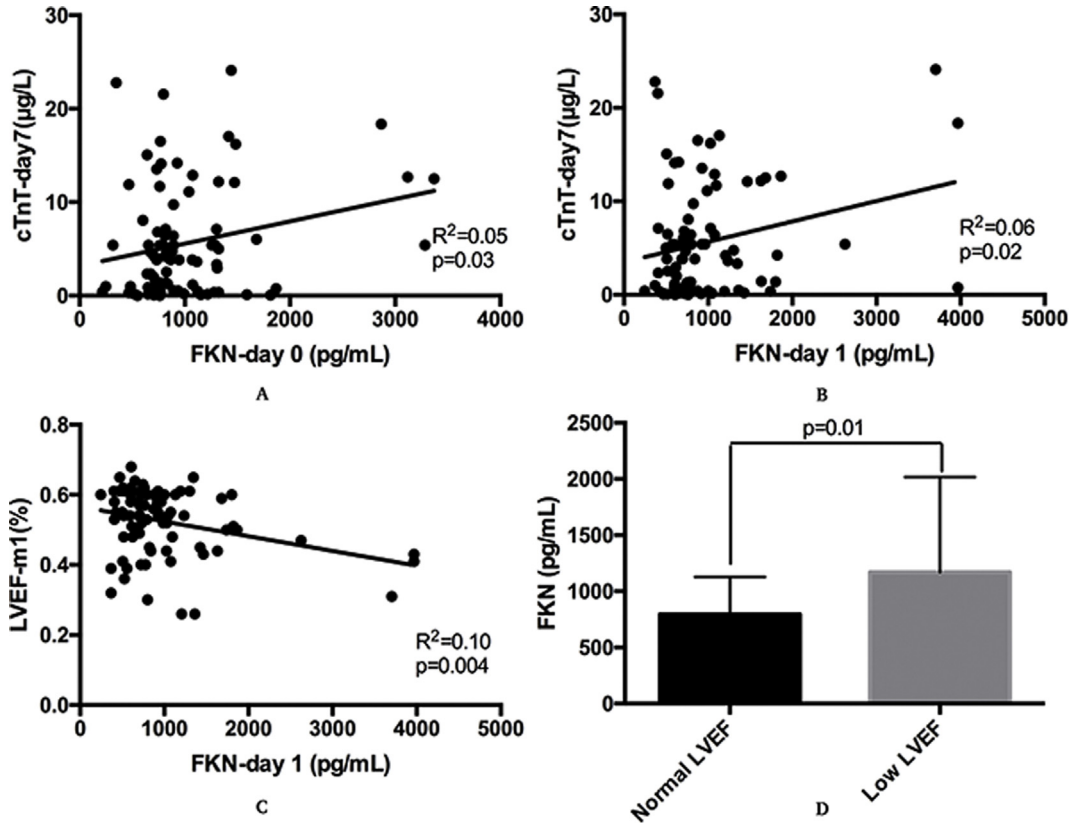

Fig. 1. Correlation between LVEF and the level of fractalkine and cTnT in patients with STEMI after primary PCI. (A and B) Cardiac TnT levels at day-7 after hospitalization were positively correlated with the levels of fractalkine at on admission (A) and the first day after PCI (B). (C) Fracatlkine concentrations at the first day after PCI were negatively correlated with LVEF in STEMI patients at 1 month. (D) Significant higher level of fractalkine at day 1 (FKN@day 1) in patients with lower LEVF at 1 month (< 55%), $p < 0.01$.

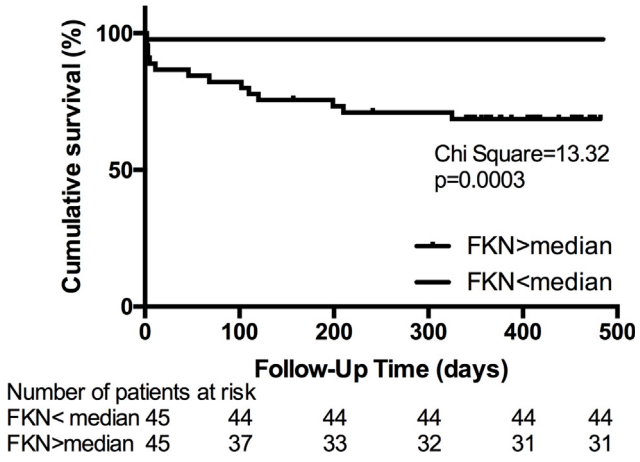

Fig. 2. Kaplan-Meier survival curves for MACE in STEMI patients. Kaplan-Meier survival curves for MACE during follow-up in STEMI patients showed high fractalkine level at day 1 after primary PCI was associated with a poorer prognosis.

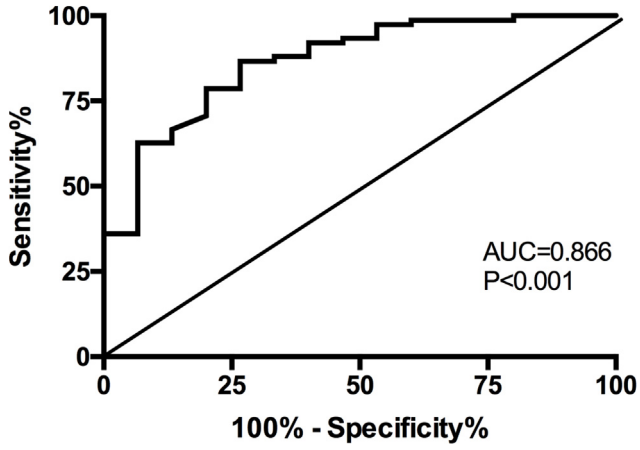

Fig. 3. Receiver operator characteristic analysis of circulating fractalkine at day-1 after primary PCI for the outcome of major adverse cardiac events (MACE) in STEMI patients.

Furthermore, the prognostic capability of FKN@day-1 for predicting MACEs is presented in Fig. 3, which has an area under the curve related to receiver operating characteristic curve of 0.867 (95% CI [0.768–0.965], p = 0.00).

Cox survival analysis was then carried out to compare the difference in survival rate between patients with different levels of FKN. The findings showed that age, 3-vessel disease, FKN@day-1, cTn-T@day-7 after hospitalization, WBC count and LVEF at 1-month after discharge were the independent predictors of MACE. Moreover, the multivariate Cox regression analysis further demonstrated that FKN@day-1 remained a significant predictor of MACE (hazard ratio [HR]: 4.63; 95% confidence interval [CI]: 1.53–14.01; p = 0.000), together with WBC count (HR: 2.73; 95% CI: 1.16–6.45; p = 0.02) and 3-vessel disease (HR: 4.74; 95% CI: 1.07–21.02; p = 0.04) (Table 3). On the contrary, neither the level of FKN measured on admission nor the DELTA FKN (day 0-day 1) showed the ability to predict the clinical outcomes after primary PCI in STEMI patients.

Table 3
Cox regression analysis for MACEs in STEMI patients after pPCI.

	Univariable analysis HR (95% CI)			Multivariable analysis HR (95% CI)		
	HR	95% CI	p value	HR	95% CI	p value
Age (year)	1.79	1.05–3.03	0.03			
three-vessel CAD	4.60	1.46–14.46	0.01	4.74	1.07–21.02	0.04
CTnT @day-7	2.52	1.28–4.94	0.01			
WBC ($\times 10^9$/L)	1.26	1.09–1.46	0.00	2.73	1.16–6.45	0.02
LVEF @1-month	0.39	0.20–0.78	0.01			
FKN@day-1, pg/mL	4.68	2.04–10.73	0.00	4.63	1.53–14.01	0.01

4. Discussion

In the present study we investigated the association between the circulating FKN and the clinical outcomes of STEMI patients after primary PCI. There are 2 main findings of our study. First, a higher level of FKN after PCI significantly increases the probability of cumulative MACE occurrence during follow-up. Second, this biomarker positively correlated with the level of cardiac Troponin T and predicts the cardiac function after AMI. To our best knowledge, no previous studies have examined FKN and its associations with left ventricular performance and future MACE in AMI patients.

Our results demonstrated that the level of circulating FKN on admission and the day after primary PCI (day-1) correlated well with high level of cardiac TnT at day 7 after primary PCI. Furthermore, the level of circulating FKN also significantly correlated with the cardiac function after 1-month of follow-up. Further regression analysis demonstrated that FKN level on the day after PCI can be a prognostic factor for cardiac function after acute myocardial fraction. In accordance with our results, Xuan et al. [21] demonstrated that FKN can promote myocardial injury and accelerates the progress of heart failure. Consequently, using neutralizing FKN antibody or resveratrol treatment can reverse cardiac pathological remodeling and improve cardiac function after myocardial infarction [21–23]. In addition, it has been described by Boag SE et al, that FKN contributes to lymphocyte shifts, which cause the development of microvascular obstruction after acute myocardial infarction through the action of effector T cells [8,10]. Accordingly, this may partially explain that why patients with higher levels of FKN after PCI had a severe cardiac injury and worse cardiac function during follow-up.

To study the effect of primary PCI on FKN, we further investigated the FKN levels before and after PCI in STEMI patients. Our results demonstrated that primary PCI resulted in an appreciable but not statically decrease in circulating FKN level within 24 h after PCI procedure. Yao et al. [24], previously reported that FKN was remarkably increased after acute myocardial infarction. However, they found that primary PCI could lead to a rapid decrease in FKN level within 6 h after the operation. The discrepancy between our and their results may because of the patients' baseline characteristics and the number of patients enrolled (20 AMI patients in their study with no MACE events documented). Surprisingly, our results demonstrated that significantly decreased circulating FKN after PCI was observed in the patients without MACE. On the contrary, the change of the level of FKN was not significant before and after PCI in those patients who had MACE occurred during follow-up. The multivariate Cox regression analysis further demonstrated that patients with higher levels of FKN at day 1 after PCI had higher incidence of cumulative MACE after AMI. Taken together, our results indicated that the level of FKN at day 1 after primary PCI might reflect the coronary artery volume (area) injury due to ischemia reperfusion after PCI, and the relationship between FKN and myocardial dysfunction and cumulative MACE after STEMI suggesting involvement of FKN in the pathogenesis after AMI. Interestingly, in agreement with previous studies [25,26], our results further exhibited that white blood cell count was also a strong predictor of MACE in STEMI patients, further strengthening the involvement of inflammation process in myocardial remodeling after AMI.

4.1. Limitations of the study

This study is a single-center study with a limited number of patients. Therefore, these findings should be treated with caution, as the number of cumulative MACE was relatively small at this time period. Further multicenter studies are warranted to enrolled more patients to verify the relationship between FKN and cumulatively MACE or each separate MACE complication respectively. Second, all of multi-vessel diseased patients in our study received culprit only revascularization during primary PCI operation. As multi-vessel disease is a strong predictor of MACE for STEMI proved by us and other studies [27,28], future work is needed to be done on revealing the relationship between fractalkine and MACE in those multi-vessel diseased patients receiving immediate complete revascularization. Third, only patients with STEMI receiving pPCI were included; thus, the results cannot be extrapolated to STEMI patients not receiving pPCI treatment or patients with NSTEMI.

In conclusion, our study demonstrated that FKN measured in STEMI patients may provide prognostic information on cardiac function and could be an independent predictor of major cardiovascular outcomes occurrence after AMI. Even more, these findings shed additional light on the pathological role of FKN in AMI complications.

Acknowledgements

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Conflict of interest

The authors have declared that no conflict of interest exists.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cyto.2018.10.006.

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