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Clinical significance of dynamic changes in hs-CRP and ADAMTS13 levels in the blood serum of patients with no-reflow after PCI operation

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Abstract. – OBJECTIVE: To evaluate the clinical significance dynamic changes in hs-CRP and ADAMTS13 levels in patients with no-reflow after PCI operation.

PATIENTS AND METHODS: 156 patients with STEMI single-vessel were enrolled in this study. Patients were divided into the reflow and the no-reflow groups. ADAMTS13 and hs-CRP levels were compared between the two groups.

RESULTS: ADAMTS13 and hs-CRP levels in the no-reflow group were significantly lower than those in the reflow group after PCI operation. The ADAMTS13 level in the reflow group peaked at 3 h and then dropped. The ADAMTS13 level was not changed significantly in the no-reflow group and reflow group before and after the operation. In the reflow group, serum hs-CRP level fell sharply within 3 h after operation, while in the no-reflow group it was decreased within 3 h to 3 days after the operation. After the operation, LVEDD was decreased significantly in both groups compared to that of before PCI, but the difference between two groups was not statistically significant. CTFC (frame) and WMSI levels in the reflow group were significantly lower than those in the no-reflow group after the operation, and the differences were statistically significant.

CONCLUSIONS: ADAMTS13 and hs-CRP levels in patients with STEMI were negatively correlated and this correlation was independent from LVDD, LVEF, BMI, WMSI, MAP, LDL, HDL and other factors which can influence STEMI reflow after the operation. Results obtained from the present study provides a valuable theoretical basis for the drug research and development as well as future studies on the no-reflow phenomenon. It also offers an important clinical application value.

Key Words:
NSTEMI, PCI, Cardiac remodeling, ADAMTS-13, hs-CRP.

Abbreviations

hs-CRP = high-sensitivity C-reactive protein; STEMI = segment elevation myocardial infarction; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricle ejection fraction; PCI = percutaneous coronary intervention; IRA = infarct related artery; TIMI = thrombolysis in myocardial infarction; BMI = body mass indexes; WMSI = wall motion score index.

Introduction

When diagnosing AMI, depending on whether ST segment of the electrocardiogram is elevated at onset, AMI can be divided into acute ST-elevation myocardial infarction (STEMI) and acute non-ST-elevation myocardial infarction (NSTEMI)[1-3]. For patients with STEMI, use of early rapid emergency thrombolysis and/or percutaneous coronary intervention (PCI) to clear coronary artery and downstream coronary artery under infarction can significantly reduce the rate of mortality and improve the prognosis[4]. However, it is possible that after PCI operation we end up with no-reflow phenomenon (no-reflow phenomenon refers to a condition in which the local tissue is without forwarding flow after PCI operation under the circumstance that IRA is located in no dissection, thrombus, spasm and distal embolization)[5]. The physiological and pathological mechanism of no-reflow is still unclear; however, some studies[6-8] have shown that no-reflow is happening due to the severe local vascular spasm, blocking and corresponding organ tissue ischemia, and release of a large number of cytokines and other factors.

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ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif), also known as von Willebrand factor-cleaving enzyme (vWFcp), is a type of zinc ion containing metalloprotein excision enzyme[9] involved in the blood clotting through vascularization of von Willebrand factor (vWF). After being secreted into the blood, it can greatly reduce VWF multimer and reduce its activity[10]. Prior studies have shown that human ADAMTS13 deficiency was firstly discovered in Upshaw-Schulman syndrome, and also more common in familial thrombotic thrombocytopenic purpura[11]. In the cases of no-reflow after PCI operation, it was shown that after the exclusion of left ventricular, diastolic diameter, blood glucose level and lipid level, ADAMTS13 can be used as an independent serum marker[12] for predicting no-reflow after PCI operation. Nevertheless, we found that the simple use of ADAMTS13 was still a relatively one-sided evaluation method. Among several patients with lower preoperative ADAMTS13, the no-reflow phenomenon was also appeared after PCI operation[13].

Hs-CRP is an ultra-sensitivity C-reactive protein, that is present in very low quantities in normal human serum, but during the inflammatory response, hs-CRP levels usually increase significantly. It is generally believed that hs-CRP has a strong prompting role on myocardial infarction and many other inflammatory diseases[14-16]. CRP is mostly synthesized through stimulating the liver cells by interleukin-6 (IL-6) and other inflammatory molecules. In our clinical findings, among many patients with no-reflow after PCI operation, CRP level showed a continuous elevation[17]. American Centers for Disease Control and Prevention (CDC) and American Heart Association (AHA) recommend that cardiovascular disease risk levels be classified according to the hs-CRP levels using the following pattern: relatively low risk (< 1 mg/L); moderate risk (1.0 to 3.0 mg/L); serious risk (> 3.0 mg/L). These indicators are considered important for evaluating no-reflow of myocardial infarction, but whether both indicators are correlated is still unclear[18]. Therefore, we combined hs-CRP and ADAMTS13 in the present study to explore their dynamic changes before and after PCI as well as the correlation between these changes in order to provide a scientific basis for the drug treatment of no-reflow phenomenon after PCI operation.

Patients and Methods

Inclusion and Exclusion Criteria

Patients inclusion criteria: All enrolled patients met the STEMI diagnostic criteria[3] developed by American College of Cardiology (ACC)/American Heart Association (AHA) and all enrolled patients had different degrees of typical pericardium area pain or discomfort, diagnosed as STEMI single vessel disease after coronary angiography examination[1]. Patients and their families signed informed consent.

Exclusion criteria[7]: (1) patients with other cardiovascular diseases such as endocarditis, valvular disease, and congestive heart failure; (2) patients under treatment with immunosuppressive medications; (3) patients with acute and chronic bacterial and/or viral infections; (4) patients with autoimmune diseases; (5) patients with connective tissue diseases; (6) patients with malignant tumors; (7) patients with liver and kidney dysfunction; (8) patients with chronic muscle diseases; (9) patients with atorvastatin allergy; (10) patients with history of surgical operation, peripheral vascular disease, chronic heart failure, thyroid disease, liver and kidney dysfunction, cancer and major trauma during 6 months prior to this study; (11) patients with myocardial infarction, a history of percutaneous transluminal coronary angioplasty and coronary artery bypass grafting within 6 months prior to this study; (12) patients under treatment with adrenocortical hormone or other immunomodulatory agents, patients deemed incapable to cope with the conditions of this research and those with a history of mental illnesses[2].

Clinical Data

From March 2014 to January 2015, 156 patients with acute coronary syndrome were enrolled in this study. There were 78 males and 78 females, aged from 48 to 77 years (mean = 62.4 ± 3.7 years).

Observation Indicator

PCI operation methods: To remove thrombus burden and to open forward flow, we used thrombus aspiration catheter within the IRA lesion segment (aspiration or suction was repeated 3 to 5 times). For forwarding flow opening, most of the intracoronary thrombus were cleared, there was no floating thrombus and contrast agent reserved continuously and IRA distal thrombus fragment residual. The

delayed angiography was carried out after 50 to 100 μg of nitroglycerin was injected into the coronary.

When the residual stenosis was less than 70% or stent passed through successfully, the stent implantation was carried out under moderate pressure (5 to 14 atm) on the sacculus and advanced dilation was achieved before implantation. Before stent implantation or sacculus predilation, during the operation, the amount of contrast agent was controlled, the number of radiography was reduced and the interval between the two times of radiography was delayed. To judge the immediate postoperative epicardial blood vessel and myocardial level perfusion, two experienced interventional cardiologists analyzed IRATIMI flow grading, thrombolysis in myocardial infarction (TIMI) frame count (CTFC) and myocardial blush grade (MBG).

Serological test: venous blood (4 to 6 ml) was collected under the empty stomach. We used 2 ml to evaluate the level of ADAMTS13 using rapid fluorescence immunoassay (Triage tester) before operation and 30 min after the operation. The remaining (2 to 4 ml) was centrifuged for 10 minutes at 1200 rpm and serum was collected and stored at -80°C. The ADAMTS13 level was tested with enzyme-linked immunosorbent assay (ELISA) 30 min after the operation.

Echocardiography test: echocardiography was performed on the patients in each group using a Philips IE33 (probe frequency 2.5 MHZ) color Doppler ultrasound diagnostic apparatus before and after the operation. LVEDD, LVESD and LVEF were recorded and the statistical analyses were conducted.

Statistical Analysis

SPSS19.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Qualitative data were analyzed using χ^2 test and quantitative data comparison was tested with analysis of variance (ANOVA). The fourfold table data not in line with the standard were tested with Fisher's probability assay. The influence factors were analyzed with Pearson correlation analysis. $p < 0.05$ indicated that the difference was statistically significant.

Results

General Clinical Data Statistics of Patients

We collected and statistically analyzed the patients' general clinical data in the reflow and the no-reflow groups, and found no significant difference in gender composition, age, fasting blood glucose, LDL, HDL, BMI, MAP and other data of patients between the two groups ($p < 0.05$) (Table I).

Comparison of Biochemical Indicators After Operation

After PCI operation, 156 patients were divided into the reflow group (98 cases) and no-reflow group (58 cases) depending on whether there was reflow after PCI operation. Statistical analyses were carried out on hs-CRP and ADAMTS13 levels in both groups, and results showed that ADAMTS13 and hs-CRP levels in the no-reflow group after PCI operation were significantly lower than the reflow group and the difference was statistically significant ($p < 0.05$) (Table II). The ADAMTS13 level in the reflow group peaked after 3 h with the ascent rate of 38.26 mg $L^{-1}h^{-1}$ and the level was dropped subsequently. ADAMTS13 levels in the no-reflow and reflow groups did not show any significant differences before and after operation ($p > 0.05$) (Figure 1). The serum hs-CRP level decreased most sharply within 3 h after operation in the reflow group (up to -8.07 $mgL^{-1}h^{-1}$). It fell sharply during 3 h to 3 days after the operation in the no-reflow group (Figure 2).

Table I. Analysis on the general clinical data.

Indicator	Sex ratio (female/male)	Age	MAP (mmHg)	LVEDD (mmHg)	LVEF	LDL (U/L)	HDL (U/L)	FPG (mmol/L)	BMI (kg/m^2)
Reflow group	44/54	58.9 ± 12.7	89.3 ± 18.6	58.3 ± 5.3	45.8 ± 4.1	2.4 ± 1.2	1.2 ± 0.8	5.6 ± 0.9	21.8 ± 1.2
No reflow group	21/37	54.5 ± 18.7	92.4 ± 27.5	57.7 ± 3.5	41.4 ± 4.5	2.7 ± 0.7	1.3 ± 0.6	5.1 ± 1.2	22.4 ± 1.8
t-value	0.02	0.35	0.16	0.48	0.63	0.24	0.45	0.38	1.14
p-value	0.34	0.25	0.28	0.34	0.41	0.44	0.69	0.29	0.48

Table II. Comparison of serum biochemical indicators in both groups before and after treatment.

Indication	Group category	Case number	Half an hour before PCI operation	Half an hour after PCI	3h after PCI	3d after PCI	F-value	p-value
ADAMTS13 (mg/l)	Reflow group	98	127.8 ± 21.8	171.3 ± 18.4	257.2 ± 16.8	202.3 ± 12.7	4.18	0.01
	No reflow group	58	132.4 ± 64.5	139.4 ± 15.9	131.7 ± 31.5	147.3 ± 32.4	0.19	0.31
	t-value	–	0.76	20.37	27.3	31.4	–	–
	p-value		0.45	0.01	0.02	0.01	–	–
Hs-CRP (mg/L)	Reflow group	98	39.7 ± 13.78	42.8 ± 11.9	22.3 ± 2.15	11.4 ± 0.83	5.74	0.01
	No reflow group	58	41.2 ± 10.65	44.2 ± 10.8	43.2 ± 1.65	23.8 ± 1.24	0.49	0.42
	t-value	–	0.82	0.39	26.4	19.8	–	–
	p-value		0.43	0.62	0.02	0.03	–	–

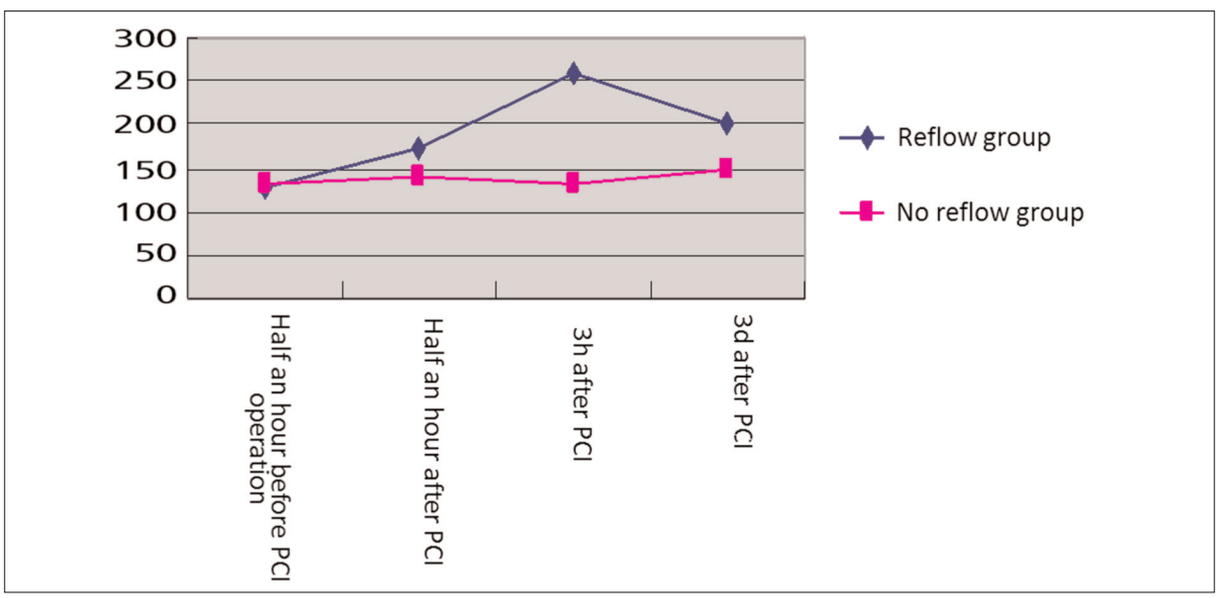

Figure 1. ADAMTS13 level broken line graph *$p < 0.05$. Serum ADAMTS13 level in the reflow group reached peak after 3 hours after operation, was increased most sharply during half an hour and 3h after operation with the ascent rate up to 38.26 mg $L^{-1}h^{-1}$. While ADAMTS13 was not significantly changed in the no-reflow group before operation

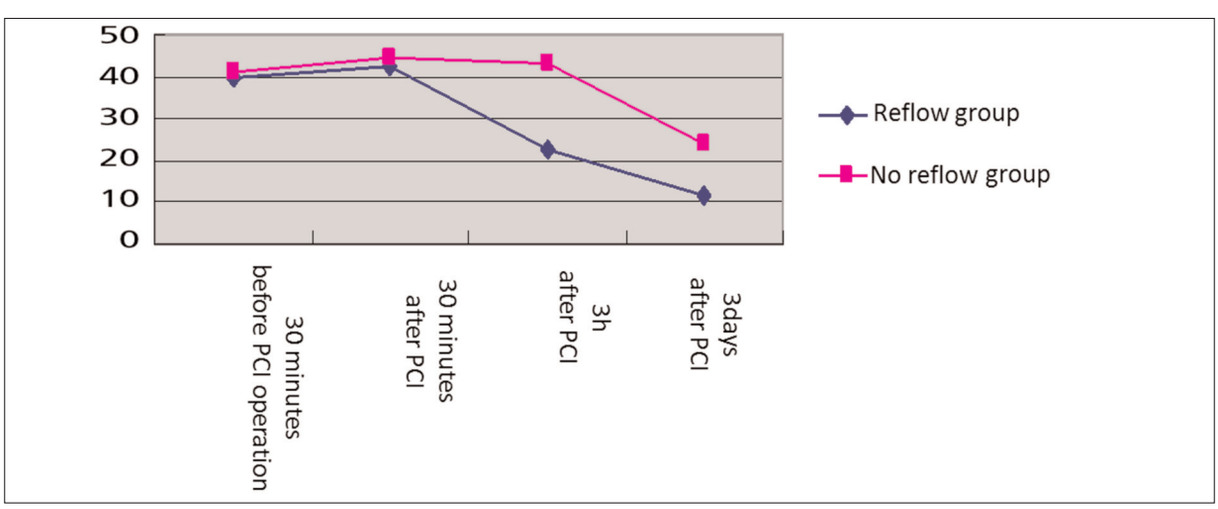

Figure 2. hs-CRP level broken line graph *$p < 0.05$ The hs-CRP level was decreased mostly sharply within 3h after operation in the reflow group, up to -8.07 $mgL^{-1}h^{-1}$, while it was decreased mostly sharply during 3h-3d after operation in the on reflow group.

Table III. Comparison of echocardiographic indicators after treatment ($\bar{x} \pm s$).

Indicators	Group category	Case number	Before PCI operation	After PCI
LVEDD (mm)	Reflow group	98	58.3 ± 5.3	52.2 ± 2.7
	No reflow group	58	57.7 ± 3.5	51.0 ± 1.5
	t-value	–	0.48	0.52
	p-value		0.34	0.25
LVESD (mm)	Reflow group	98	42.1 ± 4.7	41.2 ± 1.3
	No reflow group	58	41.8 ± 6.2	38.6 ± 1.8
	t-value	–	0.72	0.46
	p-value		0.35	0.63
LVEF (%)	Reflow group	98	45.8 ± 4.1	42.2 ± 4.5
	No reflow group	58	41.4 ± 4.5	45.3 ± 3.8
	t-value	–	0.63	0.47
	p-value		0.41	0.32

Indicators After Treatment

After PCI operation, we carried out echocardiography examination. Echocardiography results showed that LVEDD decreased significantly in both groups compared to that of before PCI, but the difference between two groups was not statistically significant ($p > 0.05$). The postoperative LVESD and LVEF in both groups increased significantly, but the difference between groups was not statistically significant ($p > 0.05$) (Table III).

Immediate Postoperative Epicardial Blood Vessels and Myocardial Level Perfusions

Results obtained from studying the immediate postoperative epicardial blood vessels and myocardial level perfusions in both groups showed that CTFC (frame) and WMSI levels in the reflow group were significantly lower than those in the no-reflow group after the operation, and the differences were statistically significant ($p < 0.05$).

Correlation Analysis Between Serum ADAMTS13 Level and Other Factors

Pearson correlation analysis showed that ADAMTS13 level was positively correlated with CTFC among patients with STEMI ($p < 0.05$) (Table V). The multivariate linear regression analysis was carried out with ADAMTS13 level as the dependent variable and the gender, age, duration of diabetes, MAP, CTF, WMSI and other indicators as independent variables. Results re-

Table IV. Immediate postoperative epicardial blood vessels and myocardial level perfusions.

Indicators	Group category	Case number	Before PCI operation	After PCI
CTFC (frame)	Reflow group	98	58.3 ± 4.3	57.2 ± 1.4
	No reflow group	58	56.7 ± 2.5	42.0 ± 1.6
	t-value	–	0.68	3.42
	p-value		0.55	0.02
WMSI (mm)	Reflow group	46	41.1 ± 3.7	39.2 ± 1.3
	No reflow group	46	40.8 ± 5.2	36.6 ± 1.8
	t-value	–	0.72	2.36
	p-value		0.35	0.03

Table V. Correlation analysis between ADAMTS13 level and clinical examination indicators.

Indicate	Gender	Age	Hs-CRP	MAP	LVEDD	LDL	HDL	CTFC	FPG	BMI	LVEF	WMSI
ADAMTS13												
r	0.02	0.35	-0.24	0.16	0.28	0.24	0.15	0.06	0.38	0.14	0.37	0.31
p	0.34	0.25	0.02	0.28	0.31	0.44	0.29	0.04	0.39	0.38	0.42	0.01

vealed that hs-CRP was most probably the influential factor on the serum level of STEMI ($p < 0.05$) (Table VI). Both of them were negatively correlated and the correlation coefficient WAS r = -0.24.-0.24.

Discussion

The occurrence of no-reflow is a common but serious complication after PCI operation. This condition mainly refers to the process that the tissue blood supply cannot be immediately restored after PCI and coronary blood flow recanalization[1,2]. Its specific mechanism is still not entirely known, but it is generally believed that no-reflow after PCI is probably related to distal micro embolization, ischemia and reperfusion injury and microcirculation injury susceptibility. The occurrence of no-reflow after PCI can reach as high as 50%, and most patients generally suffer from structural no-reflow[3], and this can seriously affect their quality of life and prognosis[4-6]. Currently, there is no effective treatment for no-reflow after PCI; therefore, prevention is the best solution[7].

ADAMTS13, also known as von Willebrand factor-cleaving enzyme (vWFcp), is a zinc ion containing metalloprotein excision enzyme involved in blood coagulation by vascularization of von Willebrand factor (vWF). After being secreted into the blood, it can greatly reduce VWF multimer and reduce its activity[9]. ADAMTS-13 and vWF levels are in dynamic equilibrium status, and when the ADAMTS-13 level is down the level of vWF polymer usually goes up. Combined with the GPIIb/IIIa complex on the platelet surface and simultaneously attached to the vascular lesion, they can cause platelet aggregation and thrombosis formation[10]. During the operation, serum ADAMTS-13 promotes the platelet aggregation and eventually clogs the capillaries in infarct area and affects the PCI effect. Results obtained in our study showed that before PCI, serum ADAMTS 13 levels in patients in both groups were not significantly different ($p > 0.05$), but after the operation, ADAMTS13 and hs-CRP in the no-reflow group after PCI were significantly lower than the reflow group. The ADAMTS13 level in the reflow group peaked after 3 h with the ascent rate of 38.26 mg $L^{-1}h^{-1}$ and dropped subsequently. In both groups, the change observed in ADAMTS13 levels before and after the operation was not statistically significant. We speculated that in the reflow group, the peak in ADAMTS13 was related to successful PCI operation, and a large quantity of ADAMTS13 locally accumulated in the infarction site into the blood circulation. While in the no-reflow group, due to local tissue thrombosis, inflammatory cell infiltration and other infarction causing factors were not lifted, and a significant delay was observed in ADAMTS13 peaking process. Meta-analysis studies[12,13] have shown that the high level of vWF was closely related to coronary heart disease in the peripheral circulation. Under the action of disintegrin, metalloproteinase and platelet type 1 modif 13 (ADAMTS13), vWF A2 structural domain can be cleaved into two parts and, as a result, the relative quality of vWF molecules is reduced, thereby inhibiting platelet aggregation function. vWF-induced platelet aggregation can be promoted under the influence of many factors such as ADAMTS13 deficiency. This can promote vWF-induced platelet aggregation, and lead to thrombotic thrombocytopenic purpura. In mouse models with thrombosis, the down-regulated ADAMTS13 could cause platelet adhesion into subendothelial matrix exposed and further cause small blood vessel damage[9] and thrombosis. Prior studies[10] have shown that the ADAMTS13 level could affect the number and/or function of vWF factor, thereby it could impact the risk of a thromboembolic event, such as myocardial infarction. In 2011, Zhao et al[6] reported that among 126 STEMI patients with

Table VI. Multiple linear regression analysis on correlation analysis between ADAMTS13 and clinical examination indicators.

Variable	β	SE	β′	*t*	*p*	(95% CI)	
						Upper limit	Lower limit
Hs-CRP	0.531	0.14	0.764	0.412	0.03	0.26	0.81
WMSI	0.581	0.10	0.642	0.652	0.28	0.39	0.78

postoperative no-reflow, von Willebrand factor levels were used as an independent factor for predicting no-reflow phenomenon. However, serum ADAMTS13 and von Willebrand factor levels were negatively correlated. Hence, the ADAMTS13 level could also be used as another evaluation factor of the no-reflow phenomenon[13].

We also observed that the serum hs-CRP level in the reflow group within 3 h after operation decreased most sharply (up to -8.07 $mgL^{-1}h^{-1}$). In the no-reflow group, serum hs-CRP level was decreased most sharply during 3 h to 3 days after the operation in the no-reflow group ($p < 0.05$). hs-CRP high-sensitivity C- reactive protein is an acute phase protein synthesized by the liver cells when the body is under microbial invasion or in the case of tissue injury and other inflammatory stimuli. Within a few hours after the occurrence of inflammation, CRP level increase significantly[14]. CRP is a highly sensitive, nonspecific, systemic inflammation, tissue injury and infection marker[15-16]. In acute coronary syndrome, CRP level can be used as the initial predictive indicator. Soylu et al[17] reported that among STEMI patients, a reduction in neutrophil/lymphocyte ratio might indicate the presence of no-reflow phenomenon after PCI. Pearson analysis showed that serum ADAMTS13 and hs-CRP levels in patients with STEMI were negatively correlated, such correlation was independent from LVDD, LVEF, BMI, WMSI, MAP, LDL, HDL and other factors which can influence STEMI reflow after the operation, and the difference was statistically significance ($p < 0.05$). Some studies have shown that hs-CRP level was positively correlated with the peripheral blood CD3 + and CD4 + T lymphocyte ratio. Thus, combining the results of the present study, after STEMI, whether the no-reflow phenomenon after PCI can be improved through adjusting the hs-CRP level secreted by liver cells in vivo, adjusting the of inflammatory cell infiltration and inflammatory factor secretion can be taken as a new study direction[18].

Additionally, we also found out that the echocardiographic indicators in some patients were roughly equal to those before the operation and even worse in few cases. This might be due to the fact that the cardiac remodeling caused by ACS was a chronic recovery process; although PCI recanalization could improve myocardial ischemia and hypoxia state and make the myocardial function recovered, the improvement in ventricular morphology would still take more time[19-23].

Conclusions

In summary, ADAMTS13 and hs-CRP levels showed a negative correlation, and the combined application of ADAMTS13 and hs-CRP levels played an important role in the evaluation of no-reflow after PCI. It could also be used as a target for drugs, by improving the preoperative ADAMTS13 level and/or reducing the hs-CRP level, it could significantly reduce postoperative adverse events. Results obtained from the present study can provide a valuable theoretical basis for the drug research and development as well as future no-reflow phenomenon studies. It also presents an important clinical application value.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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