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Original Article

Correlation between plasma D-dimer level with GRACE risk score in patients with acute non-ST-segment elevation myocardial infarction

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Abstract: Objective: To investigate the correlation between plasma D-dimer level with GRACE (Global Registry for Acute Coronary Events) risk score in patients with NASTEMI (acute Non-ST-segment elevation myocardial infarction) so as to provide a basis for improving the diagnosis and treatment of NASTEMI. Methods: 135 patients with NASTEMI admitted in our department of cardiology from June 2013 to December 2014 were included as research object. The plasma concentration of D-dimer was measured in all patients with NASTEMI on admission and GRACE score calculated and used for risk stratification. The relationships between plasma D-dimer level and GRACE score as well as risk stratification were analyzed. Moreover, their value in predicating recent adverse cardiovascular events was also analyzed. Results: The square root of D-dimer in high-risk group of patients with high GRACE risk score was higher than that in moderate-risk group and low-risk group, and that in moderate-risk group higher than that in low-risk group ($P<0.05$). The GRACE score of patients with high D-dimer level (≥1.0 μg/ml) was significantly higher than that in patients with low D-dimer level (<1.0 μg/ml) ($P<0.05$). The square root of plasma D-dimer in NASTEMI patients was positively correlated with GRACE score ($r=0.501$, $P<0.001$). 9 cases (6.7%) of cardiovascular events occurred during follow-up period. The AUC of recent cardiovascular events predicted based on plasma D-dimer in NASTEMI patients was 0.719 (SE=0.075, P=0.028, 95% CI: 0.573-0.866) and that based on GRACE score was 0.785 (SE=0.062, P=0.004, 95% CI: 0.661-0.907). The value of both indicators in predicting recent cardiovascular events in NASTEMI patients had no statistically significant difference ($P>0.05$). Conclusion: In NASTEMI patients, the higher plasma D-dimer level is, the higher GRACE score is and the higher the risk of recent cardiovascular events is. Therefore, measuring plasma D-dimer level is valuable for rapid risk assessment and prognostic prediction in NASTEMI patients.

Keywords: NSTEMI, D-dimer, GRACE risk score, correlation analysis

Introduction

Patients with acute non-ST-segment elevation myocardial infarction (NSTEMI) had big difference in clinical manifestations, various complications and poor prognosis. In order to improve the prognosis of NASTEMI patients, it was of great significance to make risk stratification, properly evaluate the severity of patients' condition and take specific measures as early as possible [1]. Currently, the most frequently used tool for risk stratification is Global Registry for Acute Coronary Events (GRACE) risk score, which can both evaluate patients' condition comprehensively and guide clinical treatment. However, for many factors are to be considered, a period of time has to be taken before results can be obtained [2, 3]. Plasma D-dimer is a kind of specific degradation product formed when cross linked fibrin is hydrolyzed by fibrinolysin. Increased plasma D-dimer indicates fibrin thrombus formation and fibrinolysis. Thus, clinically, it is usually used for identifying different types of fibrinolysis and evaluating the effect of thrombolytic therapy [4]. In recent studies, it was found that D-dimer is also valuable for the diagnosis, treatment and prognosis of cardiovascular disease: D-dimer level was closely cor-

related with the severity of coronary artery disease and the prognosis of patients with acute coronary syndrome [5, 6]. Nevertheless, up to now, few studies had been made on the correlation between D-dimer and the GRACE score in NASTEMI patients as well as the value of D-dimer in predicating cardiovascular events after discharge. In this study, a retrospective analysis was made on D-dimer level, GRACE score and cardiovascular events occurred after discharge in NASTEMI patients admitted in our hospital to investigate the correlation between D-dimer and GRACE score as well as the value of D-dimer in predicating cardiovascular events after discharge.

Information and methods

Object of study

The object of study was NASTEMI patients admitted in our hospital from June 2013 to December 2014. Inclusion criteria were as follows: (1) Consistent with the diagnostic criteria of NASTEMI [7]; (2) Clinical features and 6 months follow-up data after discharge available. Exclusion criteria were as follows: (1) Complicated by pulmonary embolism; (2) Complicated by aortic dissection; (3) With serious liver or kidney insufficiency; (4) Complicated by infection, shock or diffuse intravascular coagulation; (5) Complicated by malignant tumors. A total of 135 NASTEMI patients were included in this study, including 79 male (58.5%) and 56 female (41.5%). Their age ranged from 42 to 83 years with median age of 62 years, averaging (64.9±13.4) years.

Plasma D-dimer detection

Venous blood was taken from patients immediately after admission and citrate sodium was added for anticoagulation. After centrifuging for 15 min, plasma was separated and plasma D-dimer level was detected by using C8000 automatic biochemistry analyzer Abbot (the US) (bylatex-enhanced immunoturbidimetric assay).

GRACE score

GRACE score was obtained based on patients' clinical data [8]. The sum of GRACE score was calculated on the basis of eight aspects, namely, patients' age, heart rate, systolic arterial pressure, serum creatine, ECG ST-segment changes, heart function Killip grade, increased cardiac markers and heart arrest on admission. GRACE score ≤88 indicated low-risk, 89-118 moderate-risk and >118 high-risk.

Follow-up

Patients' follow-up data was collected by regular outpatient service and telephone calls, including cardiovascular events (recurrence of myocardial infarction, emergence of heart failure and cardiac death), follow-up time and medication. Patients were followed until cardiovascular events occurred or 6 months after discharge (the follow-up rate reached up to 100.0%). The survival time without cardiovascular events lasted from discharge to the time when cardiovascular events occurred or the last follow-up. It was expressed in months.

Study methods

Clinical features and follow-up data of admitted NASTEMI patients were collected by consulting hospitalization records, physiological and biochemical checklists, follow-up records and other medical records. Associated information was excerpted, mainly including sex, age, smoking history, diabetes and hypertension history, plasma D-dimer level, cardiac markers, ECG, emergence of heart failure within 6 months after discharge, recurrence of cardiovascular events like myocardial infarction and sudden cardiac death, follow-up time and survival time without cardiovascular events, etc.

Statistical analysis

A statistical analysis was made by using SPSS21.0 software. Plasma D-dimer fitted normal distribution after square foot transformation. Quantitative data was described as mean ± standard deviation ($\bar{x}\pm S$). *t* test and ANOVA were used for inference. Post-hoc pairwise comparison was performed by using SNK-*q* test. Relative numbers like rate and constituent ratio were used for describing qualitative data and χ^2 test for inference. Correlation analysis was made by using Pearson product-moment correlation. The value of D-dimer and GRACE score in predicating cardiovascular events within 6 months after discharge was analyzed by using receiver operator characteristic curve (ROC). The significance level was α=0.05 and P<0.05 meant that there was statistically significant difference.

Table 1. Comparison of the square root of plasma D-dimer level in NASTEMI patients with different risk stratifications

Items▼	Risk stratification			F/χ^2	P
	High-risk group	Moderate-risk group	Low-risk group		
Case number [case (%)]	53 (39.3)	45 (33.3)	37 (27.4)		
Age (year [s])	64.21±11.32	67.14±12.56	61.52±10.17	2.460	0.089
Male [case (%)]	32 (60.4)	25 (55.6)	22 (59.6)	0.252	0.882
Hypertension [case (%)]	35 (66.0)	31 (68.9)	27 (73.0)	0.489	0.783
Diabetes [case (%)]	21 (39.6)	14 (31.1)	12 (32.4)	0.904	0.636
Smoking [case (%)]	27 (50.9)	25 (55.6)	20 (54.1)	0.219	0.896
Body mass index (kg/m^2)	24.65±3.43	25.52±3.62	26.34±3.78	2.450	0.090
hs-CRP (mg/L)	8.54±4.81	6.81±3.27[a]	6.08±3.10[a]	5.151	0.007*
TC (mmol/L)	4.82±1.54	4.68±1.27	4.52±1.09	0.552	0.579
TG (mmol/L)	1.81±1.27	1.54±0.81	1.41±0.87	1.801	0.169
HDL-C (mmol/L)	1.30±0.41	1.44±0.53	1.25±0.44	1.950	0.147
LDL-C (mmol/L)	2.82±1.03	2.74±0.92	2.62±0.93	0.473	0.629
The square foot of D-dimer (μg/ml)	1.42±0.35	1.14±0.30[a]	0.89±0.23[a,b]	33.641	<0.001*

Notes: *P<0.05; [a]Compared with high-risk group, P<0.05; [b]Compared with moderate-risk group, P<0.05; ▼hs-CRP: hyper-sensitive C reaction protein; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein; LDL-C: low-density lipoprotein.

Table 2. Comparison of GRACE score in NASTEMI patients with different plasma D-dimer levels (n=135)

Items▼	Groups with different D-dimer levels		χ^2/t	P
	Low D-dimer group	High D-dimer group		
Case number [case (%)]	57 (42.2)	78 (57.8)		
Age (year [s])	62.21±11.32	66.14±12.56	1.871	0.064
Male [case (%)]	32 (56.1)	47 (60.3)	0.230	0.632
Hypertension [case (%)]	38 (66.7)	55 (70.5)	0.227	0.634
Diabetes [case (%)]	18 (31.6)	29 (34.6)	0.137	0.712
Smoking [case (%)]	25 (43.9)	47 (60.3)	3.558	0.059
Body mass index (kg/m^2)	24.71±4.35	26.21±4.92	1.836	0.069
hs-CRP (mg/L)	6.98±3.75	7.81±4.31	1.293	0.198
TC (mmol/L)	4.60±1.11	4.75±1.35	0.688	0.493
TG (mmol/L)	1.51±1.12	1.69±1.43	0.790	0.431
HDL-C (mmol/L)	1.45±0.48	1.33±0.42	1.543	0.125
LDL-C (mmol/L)	2.62±0.93	2.81±1.14	1.032	0.304
GRACE score	115.37±28.64	139.58±32.78	4.467	<0.001*

Notes: ▼hs-CRP: hyper-sensitive C reaction protein; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein; LDL-C: low-density lipoprotein; *P<0.05.

Results

Comparison of plasma D-dimer levels in NASTEMI patients with different GRACE risk stratifications

Based on GRACE score, plasma D-dimer was classified into three groups: high-risk, moderate-risk and low-risk groups. The square root of D-dimer level in high-risk groups was higher than that in moderate-risk and low-risk groups, and that in moderate-risk groups higher than that in low-risk group. The differences were both statistically significant (P<0.05). Further, the level of high sensitive C-reactive protein (hs-CRP) in high-risk group was higher than that in moderate-risk and low-risk group (P<0.05), while there was no statistically significant difference between moderate-risk group and low-risk group (P>0.05). As for other basic features, there was no statistically significant difference among groups (P>0.05) (**Table 1**).

Comparison of GRACE score in NASTEMI patients with different plasma D-dimer levels

By taking 1.0 μg/mL as a boundary line, NASTEMI patients were classified into two groups: low D-dimer group (<1.0 μg/mL) and high D-dimergroup (≥1.0 μg/mL). It was observed that the GRACE score in high D-dimer

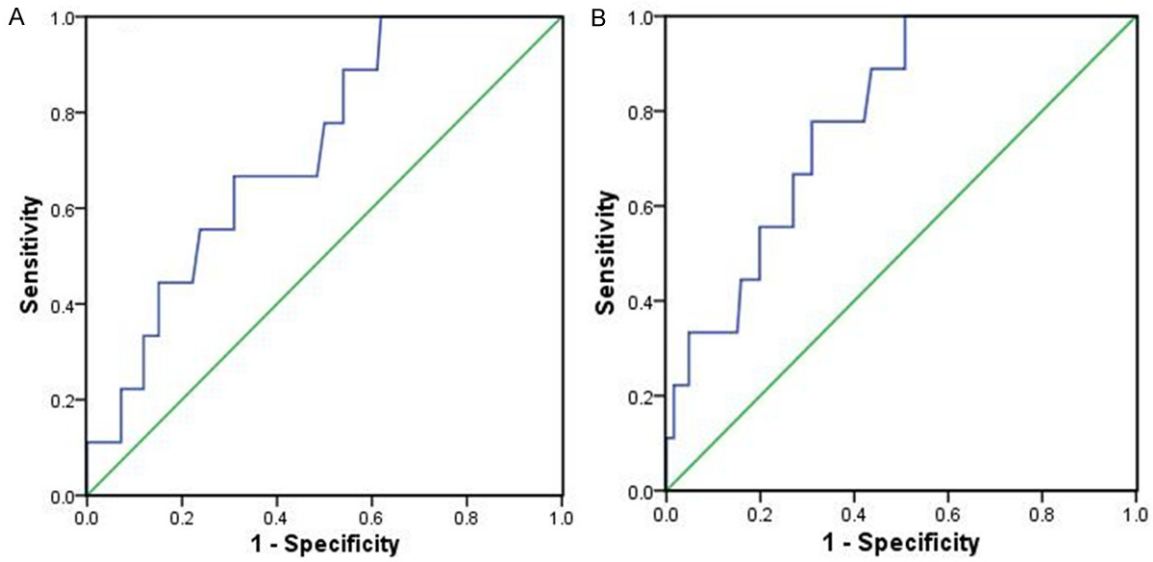

Figure 1. ROC curves of recent cardiovascular events predicted based on plasma D-dimer/GRACE score. A: Plasma D-dimer; B: GRACE score.

group was significantly higher than that in low D-dimer group (P<0.05) (**Table 2**). As for other basic features, there was no statistically significant difference between these two groups (P>0.05).

Correlation between plasma D-dimer level and GRACE score in NASTEMI patients

Pearson product-moment correlation analysis was made for the square root of plasma D-dimer and GRACE score in NASTEMI patients and results showed that the square root of plasma D-dimer was positively correlated with GRACE score (r=0.501, P<0.001).

Follow-up results

During follow-up period, there were 9 cases of cardiovascular events (6.7%), including 3 cases of myocardial infarction, 5 cases of new-onset heart failure and 1 case of sudden cardiac death. Through ROC analysis, the AUC of recent (6 months) cardiovascular events predicted based on plasma D-dimer in NASTEMI patients was 0.719 (SE=0.075, P=0.028, 95% CI: 0.573-0.866; **Figure 1A**) and that based on GRACE score was 0.785 (SE=0.062, P=0.004, 95% CI: 0.664-0.907; **Figure 1B**). Comparison of ROC curves showed that the value of both indicators in predicting recent cardiovascular events in NASTEMI patients had no statistically significant difference (P>0.05).

Discussion

NASTEMI, a common cardiovascular emergency in clinic, is characterized by atherosclerotic plaque instability, rupture, damage or internal hemorrhage and then formation of thrombus, causing acute ischemic heart disease [9]. As the most common emergency of atherosclerotic heart disease, NASTEMI is the major cause of sudden cardiac death. With the aggravation of aging population, the number of patients with coronary heart disease increases and its harm to people's health becomes more and more serious [10].

In this study, it was found that the D-dimer level in high-risk group was higher than that in moderate-risk and low-risk group and that in moderate-risk group higher than that in low-risk group. There was both statistically significant different (P<0.05). This result was similar to previous studies on patients with acute coronary syndrome [11]. It suggested that high level of D-dimer was associated with high clinical risk. According to analysis, possible reasons were as follows: Atherosclerotic plaque rupture and erosion activated coagulation and fibrinolysis followed by formation of thrombus; It was an important mechanism for the occurrence of NASTEMI; The increase of D-dimer level, a degradation product of cross linked fibrin under the effect of fibrinolysin, reflected hypercoagulable state of the body and secondary hyperfibrinoly-

sis [12, 13]. In addition, correlation analysis showed that the plasma D-dimer in NASTEMI patients was evidently correlated with GRACE score. It suggested that plasma D-dimer could be used to judge the state of illness.

Meanwhile, it was also found that there were differences in terms of hs-CRP in NASTEMI patients with different GRACE risk stratification. hs-CRP in high-risk group was higher than that in moderate-risk and low-risk group ($P<0.05$), while no statistically significant difference was found between moderate-risk group and low-risk group ($P>0.05$). By contrast, there was difference among three groups of NASTEMI patients with different GRACE risk stratification in terms of plasma D-dimer level. Plasma D-dimer level could not only differentiate high-risk patients from non-high-risk ones, but also differentiate moderate-risk ones from low-risk ones. Therefore, the consistence between plasma D-dimer and GRACE risk stratification was superior to that between hs-CRP and GRACE risk stratification.

Through ROC analysis, it was also found that the plasma D-dimer level and GRACE score in NASTEMI patients were very valuable in predicting recent (6 months) cardiovascular events and there were no obvious difference between them ($P>0.05$). The value of GRACE score in predicting recent cardiovascular events in NASTEMI patients had been demonstrated in many studies [14]. Results of this study were consistent with previous studies. Besides, it was also found that plasma D-dimer level was of predictive value for recent cardiovascular events in NASTEMI patients. This result was similar to previous studies performed in patients with acute coronary syndrome [15]. It was possibly because plasma D-dimer level could reflect the formation and size of thrombus. High D-dimer level meant that there was formation of thrombus within patient's body and the thrombus could affect the prognosis of patients [16]. The detection of plasma D-dimer was simple, economical and safe with high sensitivity. In addition, results could be obtained quickly. Therefore, by detecting plasma D-dimer rapidly, a preliminary evaluation could be performed on the risk stratification and prognosis of NASTEMI patients and emergent measures could be taken. Nevertheless, increase D-dimer was also found frequently in such diseases as pulmonary embolism, diffuse intravascular coagulation, cerebral infarction and liver cirrhosis clinically [17]. Hence, before evaluating the condition and prognosis of NASTEMI patients by D-dimer, a comprehensive analysis should be conducted to exclude associated diseases.

In conclusion, plasma D-dimer is correlated with GRACE score in NASTEMI patients: the higher plasma D-dimer level is, the higher GRACE score is. At the same time, plasma D-dimer is of predictive value for recent cardiovascular events: the higher plasma D-dimer level is, the higher risk of recent cardiovascular events is. Therefore, when other factors are excluded, plasma D-dimer can be used for risk assessment and prognostic prediction in NASTEMI patients so that specific treatment and intervention measures can be taken timely.

Disclosure of conflict of interest

None.

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