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# Relationship between Creatine Kinase and Major Bleeding in Patients with Non-ST-segment Elevation Acute Coronary Syndrome

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**Abstract**

**Background:** The present study aimed to investigate the relationship between creatine kinase (CK) and major bleeding in patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) during hospitalization.
**Objectives:** Additionally, the predictive value of CK was also analyzed for them during treatment.
**Methods:** A total of 1469 patients with NSTE-ACS, including 1024 unstable angina pectoris patients and 445 non-ST-segment elevation myocardial infarction patients, were admitted to our hospital from January 2017 to December 2019. Plasma CK and hemoglobin concentrations were measured after admission. The patients were divided into the major bleeding (n=31) and non-major bleeding (n=1438) groups according to Thrombolysis In Myocardial Ischemia bleeding classification standard, and they received routine treatment.
**Results:** Major bleeding occurred in 31 of 1469 (2.11%) patients with NSTE-ACS during the treatment period. The value of CK in the major bleeding group was higher than that of the non-major bleeding group (P<0.001). CK was divided into groups Q1- Q4 according to the quartile, and the incidence of major bleeding was higher in group Q4 than that of the other three groups (P<0.001). Plasma CK was positively correlated with major bleeding in patients with NSTE-ACS (r=0.59, P<0.001). Receiver operating characteristic curve analysis indicated that the area below the curve of baseline CK value was 0.793 (SE=0.062, P=0.001, 95%CI 0.711-0.872) in patients with NSTE-ACS during treatment.
**Conclusion:** CK was associated with major bleeding in patients with NSTE-ACS.

*Keywords:* ADP, Creatine kinase, Major bleeding, Non-ST-segment elevation acute coronary syndrome

## 1. Background

Creatine kinase (CK) is mainly present in the cytoplasm of animal tissues such as skeletal muscle, heart, and brain. Physiological processes such as intracellular energy metabolism, muscle contraction, and ATP synthesis are the other roles of CK. Also, CK affects the energy metabolism of cells by reversibly catalyzing the transphosphorylation reaction between ADP and ATP (1). CK is of great significance in activating the pathogenesis of many diseases. Major bleeding is the most common cause of non-cardiac death during treatment of non-ST-segment elevation acute coronary syndrome (NSTE-ACS) (2-4). Therefore, identifying patients who are at risk of bleeding complications during ACS treatment is significantly important. CK can inhibit ADP-dependent platelet activation and subsequent aggregation (5). During myocardial ischemia and infarction, CK enters the plasma together with cellular components such as myoglobin and troponin, as well as other small molecules including creatine phosphate (5,6). Extracellular CK can reduce ADP and inhibit the activation of ADP-dependent platelet by catalyzing the conversion of ADP to ATP. Related to this, the peak value of plasma CK during admission is closely related to bleeding after treatment of ST-segment elevation myocardial infarction (STEMI) (5). Besides, the inhibitory effect of CK on ADP-dependent platelet agglutination is considered to be synergistic with antithrombotic and thrombolytic therapy, so the level of CK may also be associated with bleeding (5).

## 2. Objectives

The present study aimed to investigate whether CK concentration independently predicts major bleeding in patients with NSTE-ACS during treatment.

## 3. Methods

### *3.1. Patients*

In this retrospective study, 1469 NSTE-ACS patients, including 1024 patients with unstable angina pectoris (UAP) and 445 patients with non-ST-segment elevation myocardial infarction (NSTEMI), were selected who were admitted to our hospital from January 2017 to December 2019. Among the 1469 patients, 851 and 618 were men and women, respectively, with a mean age of 65±9.97 years old. The median length of hospital stay was 11 (8,16) days. The patients were divided into major bleeding (n=31) and non-major bleeding (n=1438) groups according to Thrombolysis In Myocardial Ischemia (TIMI) bleeding classification standard and they received routine

treatment during hospitalization. In this study, differential diagnosis of UAP and NSTEMI was performed based on a high-sensitivity troponin assay. The reference value of high-sensitive cardiac troponin I (hs-cTnI) was 0-0.014 ug/mL. A negative hs-cTnI and positive hs-cTnI tests were diagnosed as UAP and NSTEMI, respectively. The present study was approved by the Ethics Committee of our hospital.

Inclusion criteria were patients who met the diagnostic criteria of Chinese *Guidelines for the Diagnosis and Treatment of Non-ST Segment Elevation Acute Coronary Syndrome (2016)* (7), male and non-pregnant female patients aged 18 to 80 years, and patients with stenosis of one or more vessels confirmed by coronary angiography ≥50%. Exclusion criteria included 1) Acute and chronic infectious diseases, 2) cerebrovascular diseases (a general term for brain diseases caused by various causes, including cerebral artery, cerebral vein, capillary network) injury), 3) thyroid dysfunction (includes abnormal thyroid hormones, but not normal hormone levels on active hormone replacement therapy), 4) pacemakers, 5) liver failure (including acute liver failure, subacute liver failure, acute-on-chronic liver failure, and chronic liver failure), 6) kidney failure (glomerular filtration rate <15 or on dialysis), 7) malignant tumors, 8) trauma, 9) polymyositis, 10) progressive muscular dystrophy, and 11) tetanus.

After admission, age, gender, history of hypertension, diabetes, and smoking (no smoking cessation in the past 2 months), body mass index (BMI), activated partial thromboplastin time (APTT) and platelet (PLT) of patients were recorded. The diagnostic criteria of hypertension are adults over 18 years old with systolic blood pressure ≥140 mmHg (1 mmHg=0.133 kPa), and/or diastolic blood pressure ≥90 mmHg, and/or previously diagnosed as hypertension, and/or took antihypertensive medications in the past two weeks (8). Criteria for smoking history are average smoking >1 cigarette per day, and lasting for more than half a year. Criteria for Dyslipidemia are total cholesterol (TC) >6.2 mmol/L and low-density lipoprotein (LDL) >4.1 mmol/L. Renal insufficiency is defined as glomerular filtration rate <60 mL/(min*1.73m$^2$).

On the day of admission, 3mL of intravenous heparin and 3mL of sodium citrate anticoagulant was collected from patients and sent to our hospital laboratory. The level of CK enzyme activity was determined by an automatic biochemical analyzer (BS-220, Mindray, China) and kinetic method. The concentration of hemoglobin (HGB) was determined by colorimetric analysis. PLT was detected using electrical impedance, and APTT value was assessed by an automatic blood coagulation analyzer (H1200, Jiangsu Horner Medical Instrument Co., Ltd., China). Venous blood was collected from patients on an empty stomach in the morning of the second day after admission and was sent to the laboratory. After centrifugation, serum TC, triglyceride, LDL, and high-density lipoprotein were detected. The Cobas e601 electrochemiluminescence detector and troponin I detection kits (Roche, Germany) were used in this study. Chemiluminescence immunoassay was used to detect troponin I levels in different periods, and the peak value was the maximum value ($cTNI_{max}$) in the measured samples.

classifications of TIMI bleeding are “major bleeding” in which the concentration of HGB decreases more than 50 g/L, intracranial hemorrhage or cardiac tamponade occurs, or death due to bleeding, “minor bleeding” in which the concentration of HGB decreases 30 to 50 g/L, or the patient has spontaneous gross hematuria, hemoptysis or hematemesis, “tiny bleeding” is defined as clinical bleeding (including imaging diagnosis) that can be observed, and concentration of HGB decreases to less than 30 g/L (9). In this study, "minor bleeding", "tiny bleeding", and no bleeding were generally classified as "non-major bleeding".

Coronary angiography was performed by Judkins method through radial or femoral arteries. The percutaneous transluminal coronary intervention was performed according to standard techniques. All patients were given standard secondary preventative medication according to their conditions during hospitalization.

### *3.2. Statistical Analysis*

Data were analyzed using SPSS software (version 20.0). The measurement data according to the normal distribution were expressed as mean ± standard deviation ($\bar{x} \pm sd$), and the differences between the two groups were compared using one-way ANOVA. The data that do not correspond to the normal distribution was represented by median (M) and quartile spacing (Q1, Q3), and the difference between the two groups were compared by the rank-sum test. The enumeration data were expressed as a percentage, and the difference between the two groups was compared using the Chi-squared test. Multivariate logistic regression was used to analyze the risk factors of major bleeding in patients with NSTE-ACS during treatment. The receiver operating characteristic (ROC) curve was used to analyze the predictive value of baseline CK for major bleeding in patients with NSTE-ACS during treatment, and specificity and sensitivity were also calculated. A p-value less than 0.05 was considered statistically significant.

## 4. Results

### *4.1. Comparison of clinical baseline*

There were no significant differences in the total number and classifications of bleeding between UAP and NSTEMI patients (both P>0.05). No significant differences were observed in gender, BMI, smoking, hypertension, diabetes, dyslipidemia, antiplatelet

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drugs, heparin, anticoagulants, statins, access through femoral/radial artery, and $cTNI_{max}$ between the two groups (all P>0.05). While there were significant differences in age, renal insufficiency, and serum creatinine (SCr) level between the two groups (all P<0.05). The results indicated that there was no relationship between peak troponin levels and major bleeding. See Table 1.

**Table 1.** Comparison of clinical data

| Group | Major bleeding group (n=31) | Non-major bleeding group (n=1438) | P |
|---|---|---|---|
| **Age (Year, $\bar{x}$ ± sd)** | 66.77±5.38 | 59.11±4.32 | 0.032 |
| **Male (n, %)** | 19 (61.29) | 832 (57.86) | 0.702 |
| **BMI (kg/m², $\bar{x}$ ± sd)** | 26.71±3.17 | 25.88±2.84 | 0.514 |
| **Smoking (n, %)** | 18 (58.06) | 793 (55.15) | 0.746 |
| **Hypertension (n, %)** | 23 (74.19) | 883 (61.40) | 0.147 |
| **Diabetes (n, %)** | 6 (19.35) | 261 (18.15) | 0.863 |
| **Hyperlipidemia (n, %)** | 22 (70.97) | 921 (64.05) | 0.427 |
| **APTT (s, $\bar{x}$ ± sd)** | 66.77±5.38 | 58.11±4.32 | 0.557 |
| **PLT (×10⁹/L, $\bar{x}$ ± sd)** | 207.47±52.28 | 214.60±54.08 | 0.647 |
| **Renal insufficiency (n, %)** | 6 (19.35) | 117 (8.13) | 0.026 |
| **SCr (mg/dL, $\bar{x}$ ± sd)** | 1.23±0.21 | 1.02±0.19 | 0.014 |
| **Aspirin (n, %)** | 30 (96.77) | 1413 (98.26) | 0.534 |
| **Clopidogrel (n, %)** | 31 (100.00) | 1402 (97.50) | 0.372 |
| **Statins (n, %)** | 28 (90.32) | 1233 (85.74) | 0.469 |
| **β-blockers (n, %)** | 26 (83.87) | 1214 (84.44) | 0.933 |
| **Heparin (n, %)** | 31 (100.00) | 1402 (97.50) | 0.372 |
| **Access via femoral/radial artery (n, %)** | 8 (25.81) | 417 (29.00) | 0.698 |
| **$cTNI_{max}$ (ng/L, $\bar{x}$ ± sd)** | 4.63±1.38 | 5.23±0.93 | 0.237 |

Note: BMI: body mass index; APTT: activated partial thromboplastin time; PLT: platelet; SCr: serum creatinine; cTnI: cardiac troponin I.

**Table 2.** Comparison of plasma CK values in patients with NSTE-ACS

| Group | CK (IU/L, M (Q1, Q3)) | lgCK ($\bar{x}$ ± sd) |
|---|---|---|
| **Major bleeding group (n=31)** | 750 (118, 1625.5) | 3.12±0.64 |
| **Non-major bleeding group (n=1438)** | 95 (65, 185.75) | 2.14±0.47 |
| **P** | - | <0.001 |

Note: CK: creatine kinase; NSTE-ACS: non-ST-segment elevation acute coronary syndrome.

### *4.2. Comparison of plasma CK values in NSTE-ACS patients*

The plasma CK values were skewed, and they were normally distributed after logarithmic transformation. There was a significant difference in lgCK between the two groups (P<0.001). The plasma CK value of the major bleeding group was higher than that of the non-major bleeding group (P<0.001). See Table 2.

### *4.3. Comparison of major bleeding in NSTE-ACS patients with different levels of CK*

According to the level of plasma CK, the patients were divided into 4 groups (groups Q1-Q4). There were no significant differences in gender, BMI, smoking, hypertension, diabetes, APTT, and PLT among the 4 groups (all P>0.05). The incidence of major bleeding in group Q4 was higher than that of the other three groups (all P<0.001), while there were no significant differences in the incidence of major bleeding between groups Q1 and Q2 (P=0.577), groups Q2 and Q3 (P=0.218). See Table 3.

### *4.4. Correlation between plasma CK level and major bleeding in NSTE-ACS patients*

Age, renal insufficiency, SCr level, and plasma CK level were involved in the multivariate logistic regression analysis, and the results showed that age, renal insufficiency, SCr level, and plasma CK level were independent risk factors for major bleeding in NSTE-ACS patients during treatment (all P<0. 05). See Table 4.

**Table 3.** Comparison of major bleeding in patients with NSTE-ACS with different CK levels

| Item | Group Q1 (n=367) | Group Q2 (n=368) | Group Q3 (n=367) | Group Q4 (n=367) | P |
|---|---|---|---|---|---|
| **Male (n, %)** | 201 (54.77) | 235 (63.86) | 217 (59.13) | 213 (58.03) | 0.092 |
| **BMI (kg/m², $\bar{x}$ ± sd)** | 26.88±2.34 | 25.31±3.01 | 25.17±2.79 | 25.68±2.27 | 0.274 |
| **Smoking (n, %)** | 212 (57.77) | 187 (50.82) | 199 (54.22) | 213 (58.04) | 0.159 |
| **Hypertension (n, %)** | 226 (61.58) | 244 (66.30) | 227 (61.85) | 213 (58.04) | 0.147 |
| **Renal insufficiency (n, %)** | 30 (8.17) | 33 (8.97) | 28 (7.63) | 32 (8.72) | 0.917 |
| **Diabetes (n, %)** | 71 (61.58) | 74 (61.58) | 55 (61.58) | 67 (61.58) | 0.287 |
| **APTT (s, $\bar{x}$ ± sd)** | 46±5.17 | 45±6.82 | 45±5.82 | 44±5.54 | 0.144 |
| **PLT (×10⁹/L, $\bar{x}$ ± sd)** | 213.33±45.33 | 198.67±42.98 | 202.31±53.14 | 217.47±44.35 | 0.274 |
| **Major bleeding (n, %)** | 4 (1.09) | 3 (0.81) | 5 (1.36) | 19 (5.18) | <0.001 |
| **Access via femoral/radial artery (n, %)** | 94 (25.61) | 106 (28.80) | 105 (28.61) | 120 (32.70) | 0.211 |

Note: NSTE-ACS: non-ST-segment elevation acute coronary syndrome; CK: creatine kinase; BMI: body mass index; APTT: activated partial thromboplastin time; PLT: platelet.

**Table 4.** Analysis of risk factors for major bleeding in patients with NSTE-ACS

| Factor | β | SE | Wald | 95%CI | P | OR |
|---|---|---|---|---|---|---|
| **Age** | 0.08 | 0.13 | 11.54 | 1.04-1.14 | <0.05 | 1.23 |
| **Renal insufficiency** | 1.56 | 0.75 | 5.31 | 1.09-1.67 | <0.05 | 1.74 |
| **SCr level** | 1.48 | 0.67 | 3.14 | 1.44-4.83 | <0.05 | 1.08 |
| **Plasma CK level** | 1.12 | 0.29 | 9.79 | 1.56-5.63 | <0.05 | 3.03 |

Note: NSTE-ACS: non-ST-segment elevation acute coronary syndrome; SCr: serum creatinine; CK: creatine kinase; OR: odds ratio.

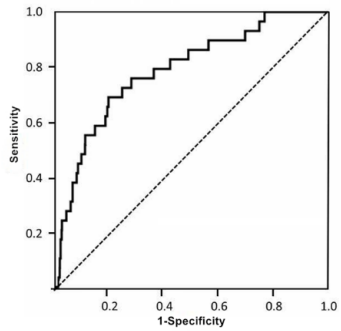


**Figure 1.** ROC curve of plasma CK level to predict major bleeding in NSTE-ACS patients during treatment
ROC: receiver operating characteristic; CK: creatine kinase; NSTE-ACS: non-ST-segment elevation acute coronary syndrome.

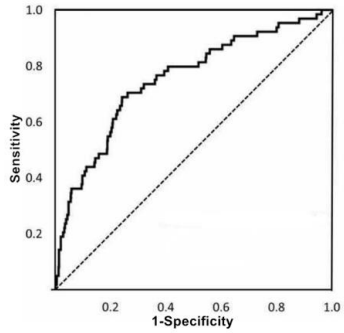


**Figure 2.** ROC curve of SCr level to predict major bleeding in NSTE-ACS patients during treatment
ROC: receiver operating characteristic; SCr: serum creatinine; NSTE-ACS: non-ST-segment elevation acute coronary syndrome.

*4.5. Effect of plasma CK on predicting major bleeding in patients with NSTE-ACS during treatment*

ROC curve analysis predicted that the area under the curve of baseline CK value was 0.793 (SE=0.062, P=0.001, 95％CI 0.711-0.872) in NSTE-ACS patients during treatment. And when the optimal critical value of plasma CK was 581.00 IU/L, it had the highest efficacy in predicting major bleeding in NSTE-ACS patients, with a sensitivity of 75.5% and a specificity of 69.3%. See Figure 1. The ROC curves for SCr level and age were shown in Figure 2 and Figure 3.

## 5. Discussion

Coronary heart disease (CHD) is one of the major diseases which threatens the health of Chinese people (10). There are many risk factors for CHD including age, gender, BMI, diabetes, hypertension, hyperlipidemia, smoking, alcohol consumption, and lack of physical exercise. CHD also has many complications and a very high mortality rate. Thrombolysis and coronary intervention are the most common clinical methods used to treat CHD. Detection of complications such as bleeding in patients during

clinical treatment has become a major clinical problem with the continuous improvement of the efficacy of antithrombotic and thrombolytic medications and a decrease in the fatality rate.

Creatine kinase (CK) consists of two subunits, which can be either B (brain type) or M (muscle type). There are three different isoenzymes, BB, MB, and MM which are mainly existed in brain tissue, myocardium, and skeletal muscle, respectively. The main function of CK is to reversibly catalyze the transfer of phosphoryl from ATP to creatine and to generate ADP and creatine phosphate, which can provide energy for various physiological activities of the organ (1,11). Clinically, CK is mainly used to diagnose myocarditis and myocardial infarction (12). In addition, the increase of CK has been confirmed in various types of muscular diseases, central nervous system diseases, cerebrovascular accidents, brain trauma, endocrine system diseases, infectious diseases, trauma, pulmonary infarction, intestinal obstruction, epilepsy and hypothyroidism, and also strenuous exercise (13-16).

The present study aimed to investigate the relationship between plasma CK and major bleeding in patients with NSTE-ACS during treatment. The results revealed that the level of plasma CK was independently associated with major bleeding in the process of NSTE-ACS, which was consistent with the findings of STEMI (5). The CK value of those with major bleeding was significantly increased compared with NSTE-ACS patients without major bleeding. When the plasma CK value was set at 581.00 IU/L, the efficacy of predicting major bleeding was highest in patients with NSTE-ACS with a sensitivity of 75.5% and a specificity of 69.3%. Age, renal insufficiency, and SCr level are other powerful independent risk factors for major bleeding in patients with NSTE-ACS (17-19).

This study still has some limitations. The patients were mostly local in this retrospective study, and their clinical data might not be completely consistent with the patients from other regions, and the sample size of patients with major bleeding during NSTE-ACS treatment was limited, and further research is needed.

## 6. Conclusion

CK was associated with major bleeding in patients with NSTE-ACS. CK as an almost obsolete enzyme in cardiology diagnosis may need to be reevaluated for its potential role in hemorrhagic complications of ACS. The detection of CK in patients with ACS can supplement the existing clinical risk assessment methods to assist clinicians in predicting the risk of major bleeding in patients with NSTE-ACS during hospitalization.

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