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THE CORRELATION BETWEEN HIGH-SENSITIVE CARDIAC TROPONIN T AND RISK STRATIFICATION BY GRACE SCORE IN PATIENTS WITH ACUTE CORONARY SYNDROME

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ABSTRACT

Background: Among all subtypes of coronary artery disease, the acute coronary syndrome (ACS) is one with high incidence, advanced severity and requires urgent medical intervention. Certain tools have been developed and used for the severity assessment and risk stratification of patients with ACS, such as the GRACE and SYNTAX and KILLIP etc. The hs-cTnT has been widely used in clinical practice for the diagnosis and prognosis prediction in ACS. The association between hs-cTnT and risk classification by GRACE has not been thoroughly investigated. **Objective**: To identify the association between hs-cTnT and risk classification by GRACE score and potential clinical utilization of serum hs-TnT in risk characterization for patients with acute coronary syndrome. **Subjects and Methods:** Medical records of 248 cases admitted to the Department of Cardiology, Zhongnan Hospital of Wuhan University were enrolled for the investigation of association between hs-cTnT and GRACE score. The baseline characteristics, medical history, laboratory tests, coronary angiography and all other required information for the analysis were extracted from the medical records. The subjects were divided as low vs. moderate/high risk group based on the GRACE score. Independent sample t test was used for the between group comparisons in terms of a continuous variable, and chi-square test was used for the between group comparisons in terms of a categorical variable. The association between hs-cTnT level and risk scores was analyzed using Spearman's correlation analysis. The multivariable logistic regression analysis was used as multivariate analysis for addressing multiple correlations simultaneously and for adjustment. A $P < 0.05$ indicated statistical significance. The SPSS 20.0 was used for statistical analyses. **Results:** Significant difference was detected between the low score and moderate / high GRACE score groups in terms of hs-cTnT (6.57 ± 7.13 pg/mL vs. 78.10 ± 101.22 pg/mL, respectively in the low score and moderate / high score groups; $P < 0.01$), total bilirubin (15.69 ± 9.38 umol/L vs. 12.95 ± 7.99 umol/L, respectively in the low score and moderate / high score groups; $P < 0.01$), BNP (52.61 ± 64.11 pg/mL vs. 78.62 ± 110.77 pg/mL, respectively in the low score and moderate / high score groups; $P < 0.05$), and left ventricular ejection fraction (64.12 ± 5.13 % vs. 62.18 ± 6.64 %, respectively in the low score and moderate / high score groups; $P < 0.05$). A strong and significant positive correlation was found between serum hs-cTnT value and GRACE score (rho = 0.63, $P < 0.01$). The result of univariate linear regression was consistent with that of Spearman correlation analysis, indicating a significantly positive association between these two variables (beta = 0.17, $P < 0.01$). Moreover, the hs-cTnT was identified as the only independent significant predicting variable for GRACE score group (beta = 0.173, $P < 0.05$) **Conclusions:** In patients with acute coronary syndrome, a higher serum hs-cTnT level is significantly and positively correlated with a higher GRACE score, and patient subgroups with increased risk as well. It is suggested the potential clinical utilization of the hs-cTnT for the risk classification in patients with acute coronary syndrome. Further clinical investigation with larger sample size, prospective design and long-term follow-up is warranted to determine its effectiveness in classification and best categorizing strategy.

KEYWORDS: Acute coronary syndrome, High-sensitive cardiac troponin T, GRACE scoring system.

INTRODUCTION

Coronary artery disease (CAD), as the most common type of cardiovascular diseases, contains a spectrum of disorders including the stable/unstable angina, myocardial infarction and sudden cardiac death. Among all subtypes of CAD, the acute coronary syndrome (ACS) is one with high incidence, advanced severity and requires urgent medical intervention.[1-3] Acute coronary syndrome is a severe medical condition which is caused by severe stenosis, deformation or rupture in one or more coronary arteries, as a result of pathologic changes caused by atherosclerosis.[4-6]

Acute coronary syndrome is generally seen in the elderly population, especially aged males and post-menopause females, and in subjects with certain health-related

conditions such as tobacco-smoking, hypertension, type II diabetes, hyperlipidemia, obesity and a family history of CAD with early onset.[3,7-15] The common manifestations of acute coronary syndrome include episodes of chest pain and chest distress which become more intensive and persisting as the disease progresses. Consequences of acute coronary syndrome vary from cardiac arrhythmia, heart failure and even sudden death. The established major risk factors for acute coronary syndrome include old age, male, abnormal metabolism of blood lipid, hypertension, cigarette smoking, type II diabetes/impaired glucose tolerance, and obesity. Recent epidemiological studies have identified new potential risk factors for acute coronary syndrome, including elevated blood homocysteine, abnormal level of fibrinogen or certain coagulation factors, infection of certain microorganisms, and history of certain inflammatory diseases.[25,38-46]

Currently, certain tools have been developed and used scoring system are two tools most widely utilized in clinical practice. The GRACE score was developed on the basis of a large-scale registry study, the Global Registry of Acute Coronary Events (GRACE), which was an international observational database designed to reflect data from an unbiased population of patients with acute coronary syndrome recruited from 200 hospitals in 28 countries from the year of 1999 to 2009. The full spectrum of patients enrolled in this study with suspected acute coronary syndrome events were included: ST-segment elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (non-STEMI) and acute coronary syndrome without biomarker release i.e. unstable angina (UA). In this study, data were collected from the first 10-20 patients admitted consecutively with suspected acute coronary syndrome per calendar month to all participating hospitals. 10% of all cases collected were audited on a regular basis to prevent case selection bias. Data were collected using an electronic case record form and forwarded to the coordinating centre, Centre for Outcomes Research, University of Massachusetts where analyses were conducted. The study was designed and administered by an independent steering committee. One of the major achievements of the main GRACE Programme was development of a clinical risk prediction tool for estimating the cumulative risk of death and or myocardial infarction to aid triage and management of patients with acute coronary syndrome.[54-58] Known as the GRACE Risk Score, this model was originally developed to estimate the risk of in-hospital mortality for patients presenting to hospital with a suspected acute coronary syndrome. The model was further developed to include prediction of mortality 6 months post discharge. Following recognition that there was a requirement for a comprehensive risk model to predict not only death, but death or myocardial infarction for up to a period of six months after hospital discharge, the GRACE Risk Score was again further developed. Eight clinical variables were involved in calculating the risk for death, and death or myocardial infarction from admission to hospital to six months after discharge. The variables taken into consideration are listed as follows: age, heart rate, systolic blood pressure, creatinine, congestive heart failure by Killip grading, cardiac arrest at admission, ST-segment deviation, and elevated cardiac biomarkers. An online application can be downloaded from the GRACE official website (http://gracescore.co.uk/) for an automated calculation of a GRACE score for a patients with acute coronary syndrome.

High-sensitive troponin T (hs-cTnT) is a novel cardiac biomarker developed on the basis of the fourth generation of cardio-specific monoclonal antibodies. The hs-cTnT has been widely applied in clinical practice and considered a sensitive and specific biomarker for the diagnosis and prognosis prediction in patients with acute coronary syndrome. The hs-cTnT has been recently investigated regarding its application and prognosis prediction for patients with acute coronary syndrome.[11,49,56,51,55]

However, currently, there is no systematic examination concerning the association between hs-cTnT and common acute coronary syndrome risk classification tools such as the GRACE score. Therefore, we performed the present retrospective study involving hundreds of Chinese subjects with acute coronary syndrome, and analyzed the association between serum hs-cTnT level and risk classification by applying the GRACE scoring system, in order to identify the potential clinical utilization of serum hs-TnT in risk characterization for patients with acute coronary syndrome.

SUBJECTS, MATERIALS AND METHODS

I. Case selection

Based on the established diagnostic criteria for acute coronary syndrome (acute coronary syndrome) as previously described , by retrospectively review the medical records, a total of 248 cases diagnosed as acute coronary syndrome and hospitalized in the Department of Cardiology and Cardiac Intensive Care Unit of the Zhongnan Hospital of Wuhan University, during the period from April 2016 to April 2017, with complete medical records and data on GRACE risk stratification, was enrolled in this part of the present study. Among the enrolled patients, 174 patients (70.2%) were male and 74 patients were female (29.8%). The median age of the enrolled patients was 61 years old, with a range of 52-75 years old. According to the clinical manifestations, findings revealed by the echocardiography (ECG) and results of laboratory tests, the subjects enrolled were furthered categorized into three subgroups, ie. the unstable angina (UA), ST elevation myocardial infarction (STEMI), and non ST elevation myocardial infarction (NSTEMI), taking into account the diagnostic standards described as follows:

1) Diagnostic criteria for unstable angina

(a) Clinical manifestations: chest pain or discomfort lasting for more than 30 minutes, which cannot be

totally alleviated by nitrate esters including the nitroglycerin. Transient third and fourth heart sound could be detected by auscultation on the apex of the heart in certain patients. On and after the ischemic attack could be detected by auscultation systolic murmur of mitral regurgitation in certain patients. Most of the patients with UA did not show obvious clinical signs.

(b) Changes in ECG: T wave inversion and non specific ST deviations could be found by ECG. The changes in ECG could disappear with symptom alleviation or persist.

(c) Laboratory test findings: Cardiac biomarkers including cardiac enzymes and troponins are generally unchanged in patients with UA.

2) Diagnostic criteria for ST elevation myocardial infarction (STEMI)

(a) Clinical manifestations: Severe chest pain persisting for more than 30 minutes, which cannot be alleviated by nitrate esters.

(b) Changes in ECG: ST elevation > 0.1mv presented in two or more neighboring leads or pathologic Q wave detected.

(c) Laboratory test findings: abnormally high measurements in cardiac biomarkers including cardiac enzymes and / or troponins.

3) Diagnostic criteria for non ST elevation myocardial infarction (NSTEMI)

(a) Clinical manifestations: Patients present with typical manifestations of angina or myocardial infarction.

(b) Changes in ECG: No signs of pathological Q waves. Could be detected sloping or horizontal depression ≥ 1mm on ST segments, as well as slightly inverted T waves.

(c) Laboratory test findings: abnormally high measurements in cardiac biomarkers including cardiac enzymes and / or troponins.

II. Inclusion and exclusion criteria

1) Inclusion criteria for the subjects with acute coronary syndrome

The subjects should meet with the established diagnostic criteria for acute coronary syndrome (acute coronary syndrome) as previously described. The interval between acute coronary syndrome onset and hospitalization should be no more than 24 hours. The age of the subjects should be between 35 and 80 years old. The subjects should be with full medical records required for the analysis in this part of the present study.

2) Exclusion criteria for the subjects with acute coronary syndrome

Subjects presenting with the following medical conditions were excluded from this study:

(1) Subjects younger than 35 or older than 80 years old.

(2) Subjects with acute coronary syndrome transformed from cor pulmonale or congenital heart diseases.

(3) Subjects with cerebrovascular diseases.

(4) Subjects with hepatic cirrhosis or chronic renal disorders, such as chronic renal failure, uremia, nephritic syndrome, etc.

(5) Subjects with malignant diseases, including any types of cancers, leukemias, etc.

(6) Subjects who had physical injury or received surgery less than two weeks before the onset of acute coronary syndrome.

III. Risk stratification of acute coronary syndrome subjects enrolled in the study

According to the ACC/AHA guidelines published in the year of 2007, the 248 subjects with acute coronary syndrome were stratified in terms of disease risk using the GRACE scoring system.[54-58] This system is based on the 6 following dimensions: i. Age; ii. Heart rate at admission; iii. Systolic blood pressure at admission; iv. Serum creatinine value at admission; v. KILLIP grading for cardiac failure at admission; vi: Presence / absence of cardiac arrest, ST segment deviations, and augmentation of cardiac biomarkers at admission. The KILLIP grades for cardiac failure were defined as follows: Grade I: No evident signs of cardiac failure; Grade II: With signs indicating left heart failure, rales on less than 50% of the pulmonary area, gallop rhythm, nodal tachycardia or other types of cardiac arrhythmias, and signs of increased pulmonary venous pressure and pulmonary congestion as shown by X ray examination; Grade III: With acute pneumonedema and / or rales on more than 50% of the pulmonary area; Grade IV: Cardiac shock, with abnormal hemodynamics of various phases and degrees. The algorithm of the GRACE scoring system was shown in Table 1. An excel application for automated calculation of the GRACE risk score was used. The subjects with acute coronary syndrome were further categorized into low risk, moderate risk and high risk subgroups. In brief, a GRACE score less than 85 was defined as low risk, a GRACE score between 85 and 133 was defined as moderate risk, and a GRACE score higher than 133 was defined as high risk.

IV. Study procedures

1. Study equipments

(1) -80 ℃ refrigerator (Hitachi, Japan).

(2) LXJ-II centrifuge (Yongcheng, China).

(3) ROCHE E411 full automatic chemiluminescence analyzer (ROCHE, Switzerland).

2. Study reagents

(1) Troponin T hs STAT (ROCHE, Switzerland).

(2) Hs-cTnT calibration reagents (ROCHE, Switzerland).

3. Hs-cTnT measurements

Peripheral blood samples were taken from study subjects within 24 hours after admission. For each subject, around 3 ml blood sample was taken into tubes containing heparin anticoagulant, and then subjected to 3500 r / min centrifugation for 7 minutes. The supernatant of the centrifuged samples were stored in -80 °C refrigerator

before analysis. The examination and measurements for hs-cTnT was performed using the Roche E411 full automatic chemiluminescence analyzer (Roche, Switzerland) and corresponding reagents.

V. Measures of interest

(1) Basic characteristics of the subjects: Age, gender, birth place, etc.
(2) Medical history of the subjects: History of angina, myocardial infarction, intervention treatment, hypertension, diabetes, smoking, etc.
(3) Clinical signs and laboratory test results related to the analysis: systolic blood pressure, diastolic blood pressure, heart rate, fasting blood glucose, serum creatinine, bilirubin, total cholesterol, triglyceride, LDL, HDL, BNP, cTnI, CK-MB, myoglobin, LVEF, hs-cTnT.
(4) Dimensions for the GRACE grading: Age, heart rate at admission, systolic blood pressure at admission, serum creatinine value at admission, KILLIP grading for cardiac failure at admission, and presence / absence of cardiac arrest, ST segment deviations, and augmentation of cardiac biomarkers at admission.

VI. Statistical analysis

The statistical analysis software SPSS version 20.0 was used for all the statistical analysis implicated in this part of the study. For continuous variables, the arithmetic average and standard deviation of the sample data were used for the descriptive analysis. For categorical variables, the count and rate of the sample data were used for the descriptive analysis. Independent sample t test was used for the between group comparisons in terms of a continuous variable, and chi-square test was used for the between group comparisons in terms of a categorical variable. The association between hs-cTnT level and GRACE score was analyzed using Spearman's correlation analysis. The multivariable logistic regression analysis was used as multivariate analysis for addressing multiple correlations simultaneously and for adjustment. A $P < 0.05$ indicated statistical significance.

RESULTS

1. Univariate comparisons in terms of clinical characteristics and laboratory test results

By retrospectively review the medical records, a total of 248 cases diagnosed as acute coronary syndrome and hospitalized in the Department of Cardiology and Cardiac Intensive Care Unit of the Zhongnan Hospital of Wuhan University, during the period from April 2016 to April 2017, with complete medical records and data for GRACE scoring, was enrolled for the investigation on the correlation between hs-cTnT and GRACE score. According to the GRACE score, 171 patients (69.0 %) with a GRACE score equal to or less than 85 were defined as the low score group, the other 77 patients (31.0 %) with a score larger than 85 were defined as the moderate / high group. The age of the subjects was 63.12 ± 9.91 years old and 65.06 ± 8.83 years old, respectively in the low score and moderate / high score groups. In the low score group, 113 (66.1%) patients were male and 58 patients (33.9%) were female. According to the results of independent sample t test and chi-square test, no significant difference was found between the low score and moderate / high score groups in terms of gender, age, systolic blood pressure, diastolic blood pressure, body mass index, heart rate, fasting blood glucose, serum creatinine, total cholesterol, triglyceride, LDL, HDL, cTnI, myoglobin, history of hypertension, history of diabetes, history of smoking, and history of drinking. Significant difference was detected between the low score and moderate / high score groups in terms of hs-cTnT (6.57 ± 7.13 pg/mL vs. 78.10 ± 101.22 pg/mL, respectively in the low score and moderate / high score groups; $P < 0.01$), total bilirubin (15.69 ± 9.38 umol/L vs. 12.95 ± 7.99 umol/L, respectively in the low score and moderate / high score groups; $P = 0.027$), BNP (52.61 ± 64.11 pg/mL vs. 78.62 ± 110.77 pg/mL, respectively in the low score and moderate / high score groups; $P < 0.021$), and left ventricular ejection fraction (64.12 ± 5.13 % vs. 62.18 ± 6.64 %, respectively in the low score and moderate / high score groups; $P = 0.013$). The summary of the group comparison analysis regarding the GRACE score is shown in Table 1.

Table 1: Summary of comparison between low and moderate/high GRACE groups.

Variables	Low score ≤ 85 n = 171	Moderate/high score > 85 n = 77	t/χ2	*P*
Age (year)	63.12 ± 9.91	65.06 ± 8.83	1.4741	0.1417
Male (%)	113 (66.1%)	49 (63.6%)	0.1402	0.708
BMI	25.02 ± 2.68	24.22 ± 4.17	1.8132	0.071
Heart Rate (per min)	75.45 ± 9.71	74.03 ± 10.88	1.0259	0.306
HBP (%)	103 (60.2%)	42 (54.5%)	0.7075	0.4003
Smoking (%)	83 (48.5%)	36 (41.6%)	0.0678	0.7946
Diabetes Mellitus (%)	40 (23.4%)	16 (20.8%)	0.2073	0.6489
Alcohol drinking (%)	58 (33.9%)	22 (28.6%)	0.6946	0.4046
Hs-cTnT	6.57 ± 7.13	78.10 ± 101.22	9.213	< 0.0001*
Fast Blood Glucose (mmol/L)	5.77 ± 1.93	5.75 ± 2.01	0.0745	0.9046
Serum Creatinine (umol/L)	77.61 ± 23.17	80.38 ± 19.64	0.9116	0.3628
Total Bilirubin (umol/L)	15.69 ± 9.38	12.95 ± 7.99	2.2249	0.027*
Total Cholesterol (mmol/L)	4.13 ± 1.63	4.16 ± 1.11	0.1468	0.8834

Triglyceride (mmol/L)	1.88 ± 1.17	1.89 ± 0.96	0.0657	0.9477
LDL (mmol/L)	2.22 ± 1.53	2.45 ± 1.22	1.1627	0.2461
HDL (mmol/L)	1.06 ± 0.18	1.07 ± 0.13	0.4385	0.6614
BNP (pg/mL)	52.61 ± 64.11	78.62 ± 110.77	2.3274	0.021*
TnI (ug/L)	0.072 ± 0.091	0.097 ± 0.138	1.6909	0.0921
LVEF (%)	64.12 ± 5.13	62.18 ± 6.64	2.5064	0.0128*

*: Statistically significant

2. The association between hs-cTnT and GRACE score by Spearman correlation analysis and univariate linear regression

According to the results of Spearman correlation analysis, a strong and significant positive correlation was found between serum hs-cTnT value and GRACE score (rho = 0.63, P < 0.01). The result of univariate linear regression was consistent with that of Spearman correlation analysis, indicating a significantly positive association between these two variables (beta = 0.17, P < 0.01).

3. Identification of independent significant predicting variables for the GRACE score by multiple linear regression

According to the results of multiple linear regression with the GRACE score as the dependant variable, three independent predicting variables were identified as independent significant predicting variables for the GRACE score, including the hs-cTnT (beta = 0.11, P < 0.01), the BNP (beta = 0.062, P < 0.05), and the bilirubin (-0.19, P < 0.05).

4. Identification of independent significant predicting variables for the GRACE score group (low score vs. moderate / high score group) by multiple logistic regression

According to the results of multiple logistic regression with the GRACE score group (low score vs. moderate / high score group) as the dependant variable, the hs-cTnT was identified as the only independent significant predicting variable for the GRACE score group (beta = 0.173, P < 0.05).

DISCUSSION

In our days, with the continuous development in economy and living standard, under the co-influence of multiple factors such as smoking, obesity, increased working pressure, lack of physical exercises, coronary artery disease has become a common healthcare concern. The incidence and mortality of coronary artery disease has been increasing in the last few years worldwide. According to the data published by Chinese Center for Disease Control, the incidence and mortality of coronary artery disease has been increasing in the last few years in China, with an overall estimated prevalence as 270 million, and caused the largest numbers of death (44.8% of death in rural areas, and 41.9% of the death in urban areas) in the year of 2013.[13,25,60,59-61] Currently, a lot of factors have been demonstrated as risk factors for coronary artery disease, including hypertension, diabetes, obesity, smoking, and hyperlipidemia. However, very interestingly, as noted in clinical practice, many patients did not have clear risk factors associated with coronary artery disease; on the other hand, certain patients having multiple risk factors associated with coronary artery disease did not develop clinically relevant disorders involving coronary arteries, or developed coronary artery disease of minor importance. Therefore, conventional risk classification based on traditional risk factors for coronary artery disease have limited predictive value and may be biased.[2,15,45,46,48,48,62-65]

In the year of 1997, investigators successfully applied the new technique for high sensitive troponin T detection in chronic heart failure patients. The new technique showed highly increased sensitivity, by which the lower limit of measurement was decreased to 10~1000 times, and fulfilled the reliability criteria that the coefficient of variation at the upper 99% percentile of the reference range less than 10%. The negative predictive value of a single test was larger than 95%. Two sequential tests taken within 3 hours of disease onset have a sensitivity of 100%. In the 2011 European Society for Cardiology clinical practice guideline for NSTE-acute coronary syndrome, the hs-cTnT has been recommended as one of the most important factors for the diagnosis and risk stratification for acute coronary syndrome. In addition to its utilization for the diagnosis and treatment of acute coronary syndrome, hs-cTnT also has an important role in prognosis prediction. According to previous research findings, a minimum level of hs-cTnT is significantly associated with long term prognosis in patients with coronary artery disease. Even in asymptomatic subjects, a minimum level of hs-cTnT is also significantly associated with long term mortality and occurrence of cardiovascular events.

For patients with chest pain as the primary complaint, a timely judgment of the condition and evaluation of the severity of coronary lesions is the key to assure that correct and beneficial medical care is taken for the patients, especially for emergency cases and areas with less developed economy. Patients with acute coronary syndrome may present various clinical manifestations, and findings of laboratory test cannot guarantee 100% correct reflection of the disease condition. The gold standard for the diagnosis and evaluation of acute coronary syndrome is the coronary angiography. However, due to the potential risks related to this invasive procedure and significant cost, only a few patients will receive coronary angiography. Therefore, to develop effective and cost-friendly strategies to achieve immediate diagnosis, severity evaluation and risk

classification in acute coronary syndrome patients is an urgent need of great importance.

According to our results, All these results consistently revealed a strong and significant positive correlation between the serum hs-cTnT level and increased risk of unfavorable outcome in patients with acute coronary syndrome as indicated by higher GRACE score, suggesting potential clinical utilization of the hs-cTnT for the risk classification in patients with acute coronary syndrome. Further clinical investigation with larger sample size, prospective design and long-term follow-up is warranted to determine its effectiveness in classification and best categorizing strategy.

CONCLUSIONS

In patients with acute coronary syndrome, a higher serum hs-cTnT level is significantly and positively correlated with a higher GRACE score, and patient subgroups with increased risk as well. It is suggested the potential clinical utilization of the hs-cTnT for the risk classification in patients with acute coronary syndrome. Further clinical investigation with larger sample size, prospective design and long-term follow-up is warranted to determine its effectiveness in classification and best categorizing strategy.

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