



**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 further categorized into three subgroups, i.e. 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 > 0.1 mv 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 ≥ 1 mm 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 pneumonema 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 °C 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/ χ^2	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 NSTEMI-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.

REFERENCES

- Dedic A, Nieman K, Hoffmann U, et al. Is there still a role for cardiac CT in the emergency department in the era of highly-sensitive troponins?[J]. *Minerva Cardioangiol*, 2017; 65(3): 214-224.
- Fu H, Vadalía N, Xue E R, et al. Thrombus leukocytes exhibit more endothelial cell-specific angiogenic markers than peripheral blood leukocytes do in acute coronary syndrome patients, suggesting a possibility of trans-differentiation: a comprehensive database mining study[J], 2017; 10(1): 74.
- Liu T, Wang G, Li P, et al. Risk classification of highly sensitive troponin I predict presence of vulnerable plaque assessed by dual source coronary computed tomography angiography[J]. *Int J Cardiovasc Imaging*, 2017; 33(11): 1831-1839.
- Zhang S J, Wang Q, Cui Y J, et al. High-sensitivity cardiac troponin T in geriatric inpatients[J]. *Arch Gerontol Geriatr*, 2016; 65: 111-5.
- Sai E, Shimada K, Miyauchi K, et al. Increased cystatin C levels as a risk factor of cardiovascular events in patients with preserved estimated glomerular filtration rate after elective percutaneous coronary intervention with drug-eluting stents[J]. *Heart Vessels*, 2016; 31(5): 694-701.
- Kavasoglu M E, Eken C, Eray O, et al. Value of High-Sensitive Cardiac Troponin in Predicting Mortality in the Emergency Department[J]. *Clin Lab*, 2016; 62(8): 1483-1489.
- Deckers J W, Zijlstra F. [Unstable angina: a diagnosis of the past][J]. *Ned Tijdschr Geneesk*, 2016; 160: A9599.
- Liebetrau C, Weber M, Tzikas S, et al. Identification of acute myocardial infarction in patients with atrial fibrillation and chest pain with a contemporary sensitive troponin I assay[J]. *BMC Med*, 2015; 13: 169.
- Kelly A M, Klim S. Does undetectable troponin I at presentation using a contemporary sensitive assay rule out myocardial infarction? A cohort study[J]. *Emerg Med J*, 2015; 32(10): 760-3.
- Kai F, Lifeng L, Haijing S, et al. [The significance of a 4,183 Da peptide of dermcidin protein in the early diagnosis and differential diagnosis of acute coronary syndrome][J]. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue*, 2015; 27(12): 970-4.
- Greenslade J H, Kavsak P, Parsonage W, et al. Combining presentation high-sensitivity cardiac troponin I and glucose measurements to rule-out an acute myocardial infarction in patients presenting to emergency department with chest pain[J]. *Clin Biochem*, 2015; 48(4-5): 288-91.
- Emrich T, Emrich K, Abegunewardene N, et al. Cardiac MR enables diagnosis in 90% of patients with acute chest pain, elevated biomarkers and unobstructed coronary arteries[J]. *Br J Radiol*, 2015; 88(1049): 20150025.
- Bonaca M P, O'malley R G, Murphy S A, et al. Prognostic performance of a high-sensitivity assay for cardiac troponin I after non-ST elevation acute coronary syndrome: Analysis from MERLIN-TIMI 36[J]. *Eur Heart J Acute Cardiovasc Care*, 2015; 4(5): 431-40.
- Sethi A, Bajaj A, Malhotra G, et al. Diagnostic accuracy of sensitive or high-sensitive troponin on presentation for myocardial infarction: a meta-analysis and systematic review[J]. *Vasc Health Risk Manag*, 2014, 10: 435-50.
- Kubo T, Kitaoka H, Yamanaka S, et al. Significance of high-sensitivity cardiac troponin T in hypertrophic cardiomyopathy[J]. *J Am Coll Cardiol*, 2013; 62(14): 1252-1259.
- Slagman A, Von Recum J, Mockel M, et al. Diagnostic performance of a high-sensitive troponin T assay and a troponin T point of care assay in the clinical routine of an Emergency Department: A clinical cohort study[J]. *Int J Cardiol*, 2017; 230: 454-460.
- Jones J D, Chew P G, Dobson R, et al. The Prognostic Value of Heart Type Fatty Acid Binding Protein in Patients with Suspected Acute Coronary Syndrome: A Systematic Review[J]. *Curr Cardiol Rev*, 2017; 13(3): 189-198.
- Kitamura M, Hata N, Takayama T, et al. Different characteristics of cardiac biomarkers to decide and predict the culprit lesions in patients with suspicious acute coronary syndrome[J]. *Heart Vessels*, 2016; 31(6): 907-17.
- Chenevier-Gobeaux C, Meune C, Lefevre G, et al. A single value of high-sensitive troponin T below the limit of detection is not enough for ruling out non ST elevation myocardial infarction in the emergency

- department[J]. *Clin Biochem*, 2016; 49(15): 1113-1117.
20. Wang X, Cai X, Chen L, et al. The evaluation of plasma and leukocytic IL-37 expression in early inflammation in patients with acute ST-segment elevation myocardial infarction after PCI[J]. *Mediators Inflamm*, 2015; 2015: 626934.
 21. Grodin J L, Neale S, Wu Y, et al. Prognostic comparison of different sensitivity cardiac troponin assays in stable heart failure[J]. *Am J Med*, 2015; 128(3): 276-82.
 22. Alevizos M, Karagkouni A, Panagiotidou S, et al. Stress triggers coronary mast cells leading to cardiac events[J]. *Ann Allergy Asthma Immunol*, 2014; 112(4): 309-16.
 23. Gupta S, Gupta V K, Gupta R, et al. Relationship of high-sensitive C-reactive protein with cardiovascular risk factors, clinical presentation and angiographic profile in patients with acute coronary syndrome: an Indian perspective[J]. *Indian Heart J*, 2013; 65(3): 359-65.
 24. Bahrmann P, Bahrmann A, Breithardt O A, et al. Additional diagnostic and prognostic value of copeptin ultra-sensitive for diagnosis of non-ST-elevation myocardial infarction in older patients presenting to the emergency department[J]. *Clin Chem Lab Med*, 2013; 51(6): 1307-19.
 25. Poldervaart J M, Rottger E, Dekker M S, et al. No Added Value of Novel Biomarkers in the Diagnostic Assessment of Patients Suspected of Acute Coronary Syndrome[J]. *PLoS One*, 2015; 10(7): e0132000.
 26. Bekler A, Barutcu A, Tenekecioglu E, et al. The relationship between fragmented QRS complexes and SYNTAX and Gensini scores in patients with acute coronary syndrome[J]. *Kardiol Pol*, 2015; 73(4): 246-54.
 27. Cubero Gomez J M, Navarro Puerto M A, Acosta Martinez J, et al. Assessment methods for aspirin-mediated platelet antiaggregation in type 2 diabetic patients: degree of correlation between 2 point-of-care methods[J]. *J Cardiovasc Pharmacol*, 2014; 64(1): 16-20.
 28. Okura H, Suzuki R, Azuma Y, et al. [The basic research on the high-sensitive troponin I assay, and the application to evaluation of chronic heart failure][J]. *Rinsho Byori*, 2013; 61(5): 375-81.
 29. Ertem A G, Bagbanci H, Kilic H, et al. Relationship between HbA1c levels and coronary artery severity in nondiabetic acute coronary syndrome patients[J]. *Turk Kardiyol Dern Ars*, 2013; 41(5): 389-95.
 30. Santi L, Farina G, Gramenzi A, et al. The HEART score with high-sensitive troponin T at presentation: ruling out patients with chest pain in the emergency room[J]. *Intern Emerg Med*, 2017; 12(3): 357-364.
 31. De Gennaro L, Brunetti N D, Locuratolo N, et al. Kounis syndrome following canned tuna fish ingestion[J]. *Acta Clin Belg*, 2017; 72(2): 142-145.
 32. Sigurjonsdottir R, Barywani S, Albertsson P, et al. Long-term major adverse cardiovascular events and quality of life after coronary angiography in elderly patients with acute coronary syndrome[J]. *Int J Cardiol*, 2016; 222: 481-485.
 33. Erxun K, Wei L, Shuying Q. Kounis Syndrome Caused by Chronic Autoimmune Urticaria: A Case Report[J]. *J Emerg Med*, 2016; 50(1): 37-40.
 34. Karadeniz M, Duran M, Akyel A, et al. High Sensitive CRP Level Is Associated With Intermediate and High Syntax Score in Patients With Acute Coronary Syndrome[J]. *Int Heart J*, 2015; 56(4): 377-80.
 35. Lippi G, Cervellin G. Do we really need high-sensitivity troponin immunoassays in the emergency department? Maybe not[J]. *Clin Chem Lab Med*, 2014; 52(2): 205-12.
 36. Van Der Laarse A, Cobbaert C M, Gorgels A P, et al. Will future troponin measurement overrule the ECG as the primary diagnostic tool in patients with acute coronary syndrome?[J]. *J Electrocardiol*, 2013; 46(4): 312-7.
 37. Gravning J, Smedsrud M K, Omland T, et al. Sensitive troponin assays and N-terminal pro-B-type natriuretic peptide in acute coronary syndrome: prediction of significant coronary lesions and long-term prognosis[J]. *Am Heart J*, 2013; 165(5): 716-24.
 38. Mockel M, Landmesser U. Challenges in using high-sensitive troponin reporting in clinical practice-The important role of appropriate use in the context of clinical evaluation[J]. *Int J Cardiol*, 2017; 245: 61-62.
 39. Cullen L, Greenslade J H, Hawkins T, et al. Improved Assessment of Chest pain Trial (IMPACT): assessing patients with possible acute coronary syndromes[J]. *Med J Aust*, 2017; 207(5): 195-200.
 40. Wang J N, Yan Y Y, Guo Z Y, et al. Negative Association of Circulating MicroRNA-126 with High-sensitive C-reactive Protein and Vascular Cell Adhesion Molecule-1 in Patients with Coronary Artery Disease Following Percutaneous Coronary Intervention[J]. *Chin Med J (Engl)*, 2016; 129(23): 2786-2791.
 41. Thorin-Trescases N, Hayami D, Yu C, et al. Exercise Lowers Plasma Angiotensin-Like 2 in Men with Post-Acute Coronary Syndrome[J], 2016; 11(10): e0164598.
 42. Shionimya H, Koyama S, Tanada Y, et al. Left ventricular end-diastolic pressure and ejection fraction correlate independently with high-sensitivity cardiac troponin-T concentrations in stable heart failure[J]. *J Cardiol*, 2015, 65(6): 526-30.
 43. Ralapanawa D M, Kularatne S A. Kounis syndrome secondary to amoxicillin/clavulanic acid administration: a case report and review of literature[J]. *BMC Res Notes*, 2015; 8: 97.
 44. Aakre K M, Langlois M R, Barth J H, et al. The quality of laboratory aspects of troponin testing in clinical practice guidelines and consensus

- documents needs to be improved[J]. *Clin Chim Acta*, 2014; 437: 58-61.
45. Parthan A, Leahy K J, O'sullivan A K, et al. Cost effectiveness of targeted high-dose atorvastatin therapy following genotype testing in patients with acute coronary syndrome[J]. *Pharmacoeconomics*, 2013; 31(6): 519-31.
 46. Mueller M, Vafaie M, Biener M, et al. Cardiac troponin T: from diagnosis of myocardial infarction to cardiovascular risk prediction[J]. *Circ J*, 2013; 77(7): 1653-61.
 47. Panovsky R, Borova J, Pleva M, et al. The unique value of cardiovascular magnetic resonance in patients with suspected acute coronary syndrome and culprit-free coronary angiograms[J]. *BMC Cardiovasc Disord*, 2017; 17(1): 170.
 48. Naz S, Ghafoor F, Iqbal I A, et al. Development of a high sensitivity C-reactive protein immunoassay and comparison with a commercial kit[J]. *J Immunoassay Immunochem*, 2017.
 49. End C, Seliger S L, Defilippi C R. Interpreting cardiac troponin results from highly sensitive assays in patients with chronic kidney disease: acute coronary syndromes and beyond[J]. *Coron Artery Dis*, 2013; 24(8): 720-3.
 50. Kubena P, Arrigo M, Parenica J, et al. Plasma Levels of Soluble CD146 Reflect the Severity of Pulmonary Congestion Better Than Brain Natriuretic Peptide in Acute Coronary Syndrome[J]. *Ann Lab Med*, 2016; 36(4): 300-5.
 51. Stopyra J P, Miller C D, Hiestand B C, et al. Performance of the EDACS-accelerated Diagnostic Pathway in a Cohort of US Patients with Acute Chest Pain[J]. *Crit Pathw Cardiol*, 2015; 14(4): 134-8.
 52. Willemsen R T, Kietselaer B L, Kusters R, et al. [Diagnostic tools for acute coronary syndrome (ACS): a challenge for general practitioners and cardiologists][J]. *Ned Tijdschr Geneesk*, 2014; 158: A8078.
 53. Han B K, Lesser A, Rosenthal K, et al. Coronary computed tomographic angiographic findings in patients with Kawasaki disease[J]. *Am J Cardiol*, 2014; 114(11): 1676-81.
 54. Zhao X Y, Li J X, Tang X F, et al. [Predictive value of GRACE discharge score for long-term out-of-hospital death in acute coronary syndrome after percutaneous coronary intervention][J]. *Zhonghua Yi Xue Za Zhi*, 2018; 98(7): 496-501.
 55. Niu X, Liu G, Huo L, et al. Risk stratification based on components of the complete blood count in patients with acute coronary syndrome: A classification and regression tree analysis[J]. *Sci Rep*, 2018; 8(1): 2838.
 56. De Carvalho L P, Fong A, Troughton R, et al. Prognostic Implications of Dual Platelet Reactivity Testing in Acute Coronary Syndrome[J]. *Thromb Haemost*, 2018; 118(2): 415-426.
 57. Chew P G, Frost F, Mullen L, et al. A direct comparison of decision rules for early discharge of suspected acute coronary syndromes in the era of high sensitivity troponin[J]. *Eur Heart J Acute Cardiovasc Care*, 2018; 2048872618755369.
 58. Araujo C, Laszczynska O, Viana M, et al. Sex differences in presenting symptoms of acute coronary syndrome: the EPIHeart cohort study[J]. *BMJ Open*, 2018; 8(2): e018798.
 59. Viana M D S, Lopes F, Cerqueira Junior A, et al. Incremental Prognostic Value of the Incorporation of Clinical Data Into Coronary Anatomy Data in Acute Coronary Syndromes: SYNTAX-GRACE Score[J]. *Arq Bras Cardiol*, 2017; 109(6): 527-532.
 60. Nieman K, Hoffmann U. Cardiac computed tomography in patients with acute chest pain[J]. *Eur Heart J*, 2015; 36(15): 906-14.
 61. Bamberg F. The Whole Is Greater Than the Sum of its Parts: Combining CT Angiography and Highly Sensitive Troponin in the Diagnostic Work-Up of Patients With Acute Chest Pain[J]. *JACC Cardiovasc Imaging*, 2015; 8(11): 1282-4.
 62. Li X, Li Y, Jin J, et al. Increased serum cathepsin K in patients with coronary artery disease[J]. *Yonsei Med J*, 2014; 55(4): 912-9.
 63. Marini M G, Cardillo M T, Caroli A, et al. Increasing specificity of high-sensitivity troponin: new approaches and perspectives in the diagnosis of acute coronary syndromes[J]. *J Cardiol*, 2013; 62(4): 205-9.
 64. George T, Ashover S, Cullen L, et al. Introduction of an accelerated diagnostic protocol in the assessment of emergency department patients with possible acute coronary syndrome: the Nambour Short Low-Intermediate Chest pain project[J]. *Emerg Med Australas*, 2013; 25(4): 340-4.
 65. Coleman C I, Limone B L. Cost-effectiveness of universal and platelet reactivity assay-driven antiplatelet therapy in acute coronary syndrome[J]. *Am J Cardiol*, 2013; 112(3): 355-62.