Original Article
The predictive values of GGT and Hcy in the risk stratifications and prognoses of NSTE-ACS patients

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Abstract: Objective: This research was designed to probe into the predictive value of glutamyltransferase (GGT) and homocysteine (Hcy) in the risk stratifications and prognoses of non-ST segment elevation acute coronary syndrome (NSTE-ACS) patients. Methods: A total of 182 NSTE-ACS patients treated with percutaneous coronary intervention (PCI) in our hospital from February 2016 to May 2018 were recruited as a patient group (PG). They were followed up for one year, and the occurrences of any major adverse cardiovascular events (MACCE) were recorded. In addition, 90 healthy volunteers were recruited as a normal group (NG) during the same period. The GGT and Hcy expressions in the serum of both groups were tested, and the predictive values of these levels, the patient risk stratification, and the prognoses were analyzed. Results: Compared with the NG, the GGT and Hcy expressions in the PG were markedly higher ($P < 0.05$). Compared with the patients without MACE, the GGT and Hcy expressions in the serum of those with MACE increased dramatically ($P < 0.05$). The serum GGT and Hcy levels were positively correlated with the NSTE-ACS patients’ SYNTAX scores ($P < 0.05$). A Kaplan-Meier curve indicated that the MACE-free survival rate of the patients with low GGT levels was dramatically higher than the survival rate of the patients with high GGT levels, and the MACE-free survival rate of low Hcy patients was significantly higher than the MACE-free survival rate of the high Hcy patients ($P < 0.05$). Our COX proportional hazards regression models indicated that the serum GGT and Hcy levels are independent predictors of MACCE in NSTE-ACS patients ($P < 0.05$). Our ROC curve analysis indicated that the serum GGT and Hcy levels are diagnostic criteria for predicting whether MACE occurred in NSTE-ACS patients. Conclusion: The serum GGT and Hcy levels are positively correlated with the severity of coronary artery disease (CAD) in NSTE-ACS patients. They are independent predictors of adverse prognoses and can help refine the risk stratification management in clinical work.

Keywords: GGT, Hcy, NSTE-ACS, diagnosis, prognosis

Introduction

Acute coronary syndrome (ACS) is a high-risk acute myocardial ischemia caused by coronary thrombosis in turn caused by the rupture of atherosclerotic plaques and is the main cause of death in developed countries. It is a subclass of coronary heart disease (CHD). According to published data, there are 15.5 million CHD patients in the United States [1], and the disease’s mortality rate in developing countries is gradually increasing [2]. NSTE-ACS is an important type of ACS, and its mechanism is mainly related to the formation and rupture of unstable coronary atherosclerotic plaque [3]. Therefore, the diagnosis, risk stratification, and management of NSTE-ACS patients are extremely important for improving the prognoses of the patients.

With the rapid development of research on serological biomarkers, many biomarkers have shown a high value in disease diagnosis and prognosis [4-6]. Therefore, in order to improve NSTE-ACS patients’ prognoses, we aimed to intensively study the related serological markers. GGT is a biomarker of liver disease. A recent study found that GGT may also be relat-
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ed to coronary artery disease (CAD), but its potential mechanism is still unclear [7]. Ndrepepa et al., [8] found that an increase in the GGT levels of ACS patients treated with PCI and statins is related to an increased risk of all-cause and non-cardiac death. Hcy is a vascular endothelial injury marker. Its increased expression can enhance oxidative stress, stimulate the growth of vascular smooth muscle cells, change the elastic properties of vascular walls, and promote thrombosis, thus participating in the development and progression of CHD, stroke, and other diseases [9-11]. The above research shows that GGT and Hcy have a great correlation with ACS. However, we don’t know the clinical significance of these two indexes in terms of CAD severity in NSTE-ACS patients, and there are few studies on NSTE-ACS patient prognosis.

Thus, this research will further examine the clinical value of the two indexes in NSTE-ACS and will provide information for patient management and treatment.

Materials and methods

Clinical data collection

A total of 182 NSTE-ACS patients who underwent PCI at Heping Hospital Affiliated to Changzhi Medical College from February 2016 to May 2018 were recruited for the study and assigned to the patient group (PG), and 90 healthy volunteers were also recruited for the study and assigned to the normal group (NG) during the same period. The inclusion criteria were as follows: patients who were diagnosed with NSTE-ACS using coronary angiography (CAG) and the diagnostic criteria of the American College of Cardiology/American Heart Association (ACC/AHA) 2012 guidelines [12], also, patients who had undergone no surgery or experienced any trauma in the most recent 6 months, patients with perfect clinical data, and patients who cooperated with the follow-up. The patients were informed of the study, and the informed consent forms were signed. The exclusion criteria were as follows: patients also suffering from a malignancy, patients with immune system diseases, infections, or a hepatic or renal insufficiency, and patients who were pregnant or lactating. This research was approved by the medical ethics committee of our hospital.

Sample collection and testing

Two groups of researchers collected 5 mL blood from a vein in patients on an empty stomach. It stood at room temperature for 30 min, then the blood was centrifuged at 3,000×g at 4°C for 10 min. The supernatant was collected and stored in a freezer at -80°C for later examination. The serum GGT was tested using an automatic biochemical analyzer (Beckman Coulter, USA, Uicel Dxc800), and the Hcy was analyzed using a full-automatic immunity chemiluminescence analyzer (Abbott, USA, Axmy).

Patient risk stratification

The patients’ risk stratification was performed based on their SYNTAX scores [13], and the complexity of their coronary arteries was quantitatively evaluated in light of their anatomical characteristics, such as the location, severity, bifurcation, and calcification of their coronary artery lesions. The high-risk patient scores were ≥ 33, the medium-risk patient scores ranged from 23-32, and the low-risk patient scores were ≤ 22.

Follow-up of patients

After the PCI treatment, all the patients were followed up for one year using telephones, the internet, and outpatient reexaminations, and the result was MACCE.

Outcome measures

The main outcome measures were as follows: the serum GGT and Hcy expressions in both groups, the serum GGT and Hcy expressions in the MACCE patients, the relationship between the patients’ serum GGT, Hcy, and SYNTAX scores, the COX regression analysis of the independent risk factors of MACCE, the ROC curve analysis of GGT and Hcy in predicting the post-operative MACCE.

The secondary outcome measures were as follows: the relationship between the serum GGT, Hcy, and survival without MACCE. The serum GGT and Hcy expressions in patients with different numbers of diseased coronary arteries were observed.

Statistical analysis

The collected data were analyzed statistically using SPSS 23.0 (SPSS Co., Ltd., Chicago, U.S.).
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Results

Comparison of the general clinical data

The data in Table 1 shows that there were no significant differences in terms of age, gender, BMI, history of smoking and drinking, place of residence, or the laboratory indicators between the two groups (P > 0.05), so they were comparable.

The serum GGT and Hcy expressions in both groups

We found that the serum GGT and Hcy expressions in the patients in the PG were dramatically higher than the serum GGT and Hcy expressions in the NG (P < 0.001) (Figure 1).

The relationship between the serum GGT and Hcy expressions and MACCE

All the patients were followed up for one year. The data showed that 26 patients developed MACCE within one year (14.29%). The patients were then assigned to a MACCE group or a MACCE-free group. Comparing the serum GGT and Hcy expressions in both groups, we found that the serum levels in the MACCE group were dramatically higher than they were in the MACCE-free group (P < 0.001) (Figure 2).

The serum GGT and Hcy expressions in the patients with different numbers of diseased coronary arteries

According to the number of coronary artery lesions, there were 62 patients in the single-vessel disease group, 69 with two-vessel disease, and 51 with multi-vessel disease. By comparing the GGT and Hcy expressions among the three groups, we found that the serum GGT and Hcy expressions in the two-vessel disease group were higher than they were in the single-vessel disease group (P < 0.001), and the expressions in the multi-vessel disease group were higher than they were in the two-vessel disease group (P < 0.001) (Table 2).

The relationship between the serum GGT and Hcy levels and the MACCE-free survival of patients

Taking into account their median expressions of GGT and Hcy, the patients were assigned to low expression and high expression groups, and the MACCE-free survival rate of the patients

Table 1. The general clinical data

<table>
<thead>
<tr>
<th>Factor</th>
<th>Normal group (n = 90)</th>
<th>Patient group (n = 182)</th>
<th>t/X² value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65.72±8.41</td>
<td>66.25±8.63</td>
<td>0.480</td>
<td>0.631</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>42 (46.67)</td>
<td>102 (56.04)</td>
<td>2.126</td>
<td>0.145</td>
</tr>
<tr>
<td>Female</td>
<td>48 (53.33)</td>
<td>80 (43.96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.67±2.28</td>
<td>22.12±1.98</td>
<td>1.676</td>
<td>0.095</td>
</tr>
<tr>
<td>History of smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>56 (62.22)</td>
<td>131 (71.98)</td>
<td>2.668</td>
<td>0.102</td>
</tr>
<tr>
<td>No</td>
<td>34 (37.78)</td>
<td>51 (28.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of alcoholism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>64 (71.11)</td>
<td>145 (79.67)</td>
<td>2.479</td>
<td>0.115</td>
</tr>
<tr>
<td>No</td>
<td>26 (28.89)</td>
<td>37 (20.33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Place of residence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>City</td>
<td>49 (54.44)</td>
<td>88 (48.35)</td>
<td>0.894</td>
<td>0.344</td>
</tr>
<tr>
<td>Countryside</td>
<td>41 (45.56)</td>
<td>94 (51.65)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>4.78±0.88</td>
<td>4.85±0.64</td>
<td>0.746</td>
<td>0.456</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>0.98±0.46</td>
<td>1.02±0.31</td>
<td>0.847</td>
<td>0.398</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>3.11±0.54</td>
<td>3.15±0.49</td>
<td>0.612</td>
<td>0.541</td>
</tr>
</tbody>
</table>
GGT and Hcy in NSTE-ACS patients

The serum GGT and Hcy expressions in both groups. A. The serum GGT expressions in the patient group were significantly higher than they were in the normal group; B. The serum Hcy expressions in the patient group were dramatically higher than they were in the normal group. ***denotes \( P < 0.001 \).

Figure 1.

The relationship between the serum GGT and Hcy expressions and MACCE. A. The GGT expressions of the patients in the MACCE group were significantly higher than the expressions in the patients without MACCE; B. The serum Hcy expressions in the patients in the MACCE group were significantly higher than the serum Hcy expressions in the patients without MACCE. ***denotes \( P < 0.001 \).

Figure 2.

in the GGT low expression group was significantly higher than it was in the high expression group (\( P = 0.004 \)), but the survival rate in the Hcy low expression group was markedly higher than it was in the high expression group (\( P = 0.034 \)) (Figure 4).

A COX regression analysis of the MACCE independent risk factors

A COX regression analysis was performed with whether the patients developed MACCE as a dependent variable and their clinical data as independent variable. The results determined that age, LVEF, GGT, and Hcy were risk factors for patients to develop MACCE, but the latter three were independent risk factors (Table 3).

The predictive values of the serum GGT and Hcy levels in MACCE patients after PCI

The diagnostic value of the GGT and Hcy collected from the patients in the MACCE and MACCE-free groups was analyzed using ROC curves. The areas under the GGT and Hcy curves were 0.842 and 0.821, respectively (Figure 5).

Discussion

The increasing ACS morbidity and fatality rates seriously threaten people’s lives, and the age of incidence is gradually becoming younger. It has attracted more and more societal attention. PCI is considered the most effective method to treat ACS, but stent thrombosis and serious complications may occur without proper treatment and management [14]. Therefore, early risk assessment is of great significance for patient treatment and prognosis [15]. It’s a hot spot in modern clinical research. Serological biomarkers have made great contributions to the diagnosis,
GGT and Hcy in NSTE-ACS patients

This research probed into the relationship between GGT, Hcy, and the risk stratification of NSTE-ACS patients, and the value of using these two indicators in prognosis.

GGT is implicated in the development of atherosclerotic plaques and in the oxidation and inflammation of platelets [16]. Demirelli et al. [17] pointed out that GGT is relevant to the morbidity and mortality of cardiovascular diseases, and can be employed as a diagnostic biomarker of troponin positivity in ACS patients. Hcy is also associated with platelet activation, and it also increases inflammation, so it is considered to be a risk factor for the development of atherosclerosis [18]. In view of the great similarity between the two indicators, this study first measured the serum expressions of the two indicators and found that GGT and Hcy were remarkably up-regulated compared with healthy people. Wei et al. [19] proposed that serum Hcy expression is increased in female ACS patients, so it is a potential predictor of MACCE in patients. Zheng et al. [20] also discovered that GGT is highly expressed in the serum of ACS patients, so it can be employed as a predictor of adverse complications after PCI. All of the above studies are similar to ours, and all of them studied highly expressed GGT and Hcy levels. This also suggests that GGT and Hcy might be employed as diagnostic indicators of NSTE-ACS. The SYNTAX score is a CAD risk stratification method, and it systematically calculates the score based on the coronary angiography results, thus guiding the clinical treatment and judging the prognosis [21, 22]. Han et al. [23] found that the GGT and Hcy levels are related to the degree of coronary artery stenosis in elderly CHD patients. The higher the SYNTAX score, the more complex the CAD is. It often indicates a higher incidence of adverse prognoses [24]. We studied the relationship between the scores and the GGT and Hcy expressions. Our Pearson test analysis showed that, with an increase in the SYNTAX scores, the GGT and Hcy levels also increased, and they were positively correlated. Afterwards, we compared the serum GGT and Hcy expressions in the patients with different numbers of diseased coronary arteries. It was found that the serum GGT and Hcy expressions in the two-vessel disease group were higher than the serum GGT and Hcy expressions in the single-vessel disease group, and the expres-

Table 2. The serum GGT and Hcy expressions in patients with different numbers of diseased coronary arteries

<table>
<thead>
<tr>
<th>Groups</th>
<th>GGT</th>
<th>Hcy</th>
</tr>
</thead>
<tbody>
<tr>
<td>single-vessel disease group (n = 62)</td>
<td>29.15±5.63</td>
<td>18.75±3.04</td>
</tr>
<tr>
<td>two-vessel disease group (n = 69)</td>
<td>33.87±5.46*,#</td>
<td>22.67±3.25*,#</td>
</tr>
<tr>
<td>multi-vessel disease group (n = 51)</td>
<td>38.31±6.12*,</td>
<td>26.64±3.58*</td>
</tr>
<tr>
<td>F</td>
<td>36.25</td>
<td>81.34</td>
</tr>
<tr>
<td>P</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Note: * means the comparison with the single-vessel disease group (P < 0.05); # means the comparison with the multi-vessel disease group (P < 0.05).
Tensions in the multi-vessel disease group were higher than the expressions in the two-vessel disease group. The above results show that the GGT and Hcy levels can predict the SYNTAX scores and the numbers of diseased coronary arteries, and this data can be used as the basis for risk stratification and provide a sufficient clinical basis for preoperative risk assessment.

MACCE is an important cause of high morbidity and mortality after operations [25], and it seriously affects patient prognosis. Hence, this research deeply discusses the occurrence of MACCE after operations in NSTE-ACS patients and the relationship between GGT and Hcy and provides a basis for the treatment and improvement of prognosis in the future. The GGT and Hcy levels in the serum of patients with and without MACCE after their operations were statistically analyzed. It was found that the serum GGT and Hcy levels in patients without MACCE were significantly lower than the serum GGT and Hcy levels in the patients with MACCE. This suggests that GGT and Hcy might be potential biological indicators for diagnosing MACCE. Then, through a survival analysis curve, we found that the MACCE-free survival rates of the patients with low expressions of GGT and Hcy were markedly higher than the survival rates of those with high expressions, which indicated that the two might also be potential biological indicators for predicting the prognosis of NSTE-ACS patients. According to our COX proportion-
In general, the serum GGT and Hcy levels are positively correlated with the severity of CAD in NSTE-ACS patients. They are independent predictors of an adverse prognosis, and they can assist in refining risk stratification management in clinical work.

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Disclosure of conflict of interest

None.

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