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*Original Article*

# Effect of self-made blood stasis-expelling decoction on liver function and cardiovascular events in patients with non-ST-segment elevation acute coronary syndrome

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**Abstract:** Objective: To investigate the effect of self-made blood stasis-expelling decoction (BSD) on liver function and cardiovascular events in patients with non-ST-segment elevation acute coronary syndromes (NSTE ACSs) as well as statin-induced elevation of aminotransferase levels (SEALs). Methods: 103 patients with NSTE ACS and SEALs were randomly divided into the control group (CG, n = 51) that underwent ezetimibe treatment, and the observation group (OG, n = 52) that received additionally self-made BSD for 3 months. The following indicators were compared, including the efficacy, total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBiL), phosphocreatine kinase (CK), creatine kinase isoenzyme (CPK-MB), and the incidence of cardiovascular events. Results: The clinical efficacy of the OG was remarkably higher than that of the CG (P<0.05). The two groups showed significantly reduced post-treatment TC, TG, and LDL-C levels; In comparison of the CG, the above indicators in the OG improved more significantly (P<0.05); After treatment, ALT, AST, TBiL, CK, and CK-MB in both groups were significantly decreased (P<0.05); The above indicators in the OG were significantly deceased in comparison with CG (P<0.05); The total incidence of cardiovascular events in OG was 9.62% (5/52) which was significantly lower than 33.33% (17/51) of CG (P<0.05). Conclusion: Self-made BSD can significantly improve myocardial damage, effectively regulate blood lipid levels, improve liver function and reduce cardiovascular events in patients with NSTE ACS and SEALs.

**Keywords:** NSTE ACSs, self-made BSD, statin-induced elevation of aminotransferase levels, liver function, cardiovascular events

## Introduction

Non-ST segment elevation acute coronary syndromes (NSTE ACS) involve a clinical spectrum ranging from unstable angina (UA) to non-ST-segment elevation myocardial infarction (NSTEMI), with high morbidity and mortality [1, 2]. If early and effective clinical interventions are not implemented, it may induce major adverse cardiac events (MACE) and a poor prognosis. Coronary atherosclerosis is the main pathological basis of ACS, and hyperlipidemia is the crucial risk factor for ACS. Studies have shown that [3, 4] lipid-lowering treatment can accelerate plaque regression, lower the mortality of ACSD, effectively prevent the progression of atherosclerotic lesions, and reduce the incidence of MACE. Therefore, lipid-lowering therapy has become an important component of ACS treatment. Statins are commonly used to treat non-ST-segment elevation ACS [5, 6].

Although it has overt lipid-lowering effect, side effects such as liver damage and elevated transaminase levels are also common. In severe cases, liver-protective treatment should be supplemented [7, 8]. The incidence of elevated transaminases levels by statins is about 0.5%-3%. Previous studies [9] suggested discontinuing statin medications, hepatoprotective treatment, and used ezetimibe as an alternative lipid-lowering therapy. However, the overall efficacy was not satisfactory. Cho et al [10] found that Tongxinluo capsules is a drug composed of traditional Chinese herbs and insects used for cardiovascular diseases, which can

effectively decease lipids and hs-CRP levels, and reduce cardio-cerebrovascular events and rehospitalization rates. Traditional Chinese medicine believes that the pathogenesis of this disease lies in deficiency of qi, blood stasis, phlegm turbidity and stagnation of qi, and the treatment should focus on protecting liver and benefiting qi, regulating qi and activating blood circulation, and removing turbidity and stasis. Based on this, our study explored the efficacy of self-made BSD on NSTE ACS patients with SEALs, and its effects on liver function and cardiovascular events.

## Material and methods

### *Baseline data*

We enrolled 103 NSTE ACS patients with SEALs from January 2017 to June 2019. The patients aged below 79 years. The diagnosis of ACS is based on the diagnostic criteria established by the American College of Cardiology and the American College of Cardiology. After treatment with statins, there is a 3-fold increase in transaminases and alanine aminotransferase.

All patients did not have any history of liver disease such as chronic hepatitis B, hepatitis A, and liver tumors. For the standpoint of Traditional Chinese medicine. All patients exhibited syndrome of phlegm and blood stasis: tightening, choking or heavy pressure feeling in the cheat, shortness of breath, heavy head and legs, greasy or slippery tongue coating, and slippery pulse. The patient has clear consciousness and signed the consent form. This study was conducted under the approval of the Ethics Committee of the Second Affiliated Hospital of Kunming Medical University. Patients with liver damage caused by malignant tumors, with acute cerebrovascular diseases, and cognitive dysfunction were excluded. 103 patients with NSTE ACS and SEALs were randomly divided into the observation group (OG, n = 52, aged 42-78 years, BMI 18.55-37.06 kg/m$^2$ and control group (CG, n = 51, 45-79 years, BMI 18.53-36.95 kg/m$^2$).

## Methods

### *Inclusive and exclusive criteria*

Inclusive criteria: Patients who conformed to the above diagnostic standards; who aged between 18 and 80 years; and who were conscious and signed the written consent form. Exclusion criteria: Patients who were complicated with malignant tumor, acute cerebrovascular disease, cognitive dysfunction and other causes of liver damage; who were allergic to the drugs used in our study; who were pregnant or lactating; who were taking immunosuppressive drugs; and who had poor compliance and didn't cooperate with the study.

### *Treatment methods*

Statins were discontinued in both groups and hepatoprotective drugs were given. The CG was given oral ezetimibe tablets, 10 mg/d. The OG was additionally given self-made BSD. The self-made BSD in this trial consisted of astragalus 30 g, codonopsis 20 g, 15 g for each of the following ingredients, including angelica, danshen root, Chinese thorowax root, taxonomy browser, szechuan lovage rhizome, and radix cyathulae; 10 g each of submature bitter orange, pinellia, radix rehmanniae, and safflower, panax notoginseng powder 7 g, licorice 6 g. The decoction was boiled in a dose of 400 ml (Pack of 2 200 ml), and is taken twice in the morning (200 ml) and at evening (200 ml), lasting for 3 months. During the treatment, blood lipids, liver function and other indicators were monitored.

## Outcome measurement

### *Clinical efficacy*

Remarkable effective: ECG showed ST segment elevation ≥0.1 mV and improvement in their angina ≥2; Effective: ECG showed ST segment elevation ranged from 0.05 to 0.1 mV, improvement in their angina = 1; ineffective: ST segment elevation was less than 0.05 mV and angina did not improve or worsen. Total efficiency = 100%-inefficiency.

### *Blood lipid levels*

After fasting for 10 hours, 5 ml of venous blood was collected from patients before and after treatment, and the patients' cholesterol (TC) and triglyceride (TG) were detected by oxidase method. The serum high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) levels were measured by endpoint assay.

**Table 1.** Baseline data (mean ± SD, n)

| Group | n | Gender | | Age (year) | BMI ($kg/m^2$) | Smoking | Dring | Stains | | | | Hepatoprotective drugs | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Male | Female | | | | | Atorvastatin | Rosuvastatin | Simvastatin | other | Glucuronolactone | Polyene phosphatidylcholine capsules | Glutathione |
| Observation group | 52 | 32 | 20 | 59.05±6.23 | 27.26±2.82 | 25 | 36 | 35 | 9 | 6 | 2 | 25 | 22 | 21 |
| Control group | 51 | 30 | 21 | 58.29±6.67 | 27.05±2.68 | 28 | 32 | 31 | 12 | 5 | 3 | 23 | 21 | 19 |
| $\chi^2$/t | | 0.079 | | 0.598 | 0.387 | 0.480 | 0.483 | | 0.952 | | | | 0.016 | |
| P | | 0.778 | | 0.551 | 0.699 | 0.488 | 0.487 | | 0.813 | | | | 0.992 | |

**Table 2.** Efficacy of two groups [n (%)]

| Group | n | Markable effective | Effective | Ineffective | Effective rate |
|---|---|---|---|---|---|
| Control group | 52 | 20 (36.54) | 28 (53.85) | 4 (7.69) | 92.31① |
| Observation group | 51 | 16 (31.37) | 23 (45.10) | 12 (23.53) | 76.47 |
| $\chi^2$ | - | - | - | - | 4.921 |
| *P* | - | - | - | - | 0.027 |

①Compared with control group, *P<0.05.*

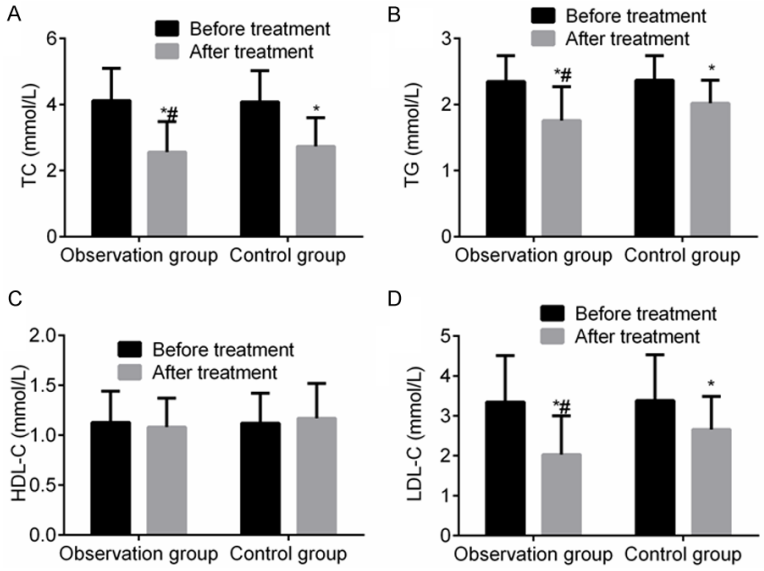


**Figure 1.** Comparison of blood lipid levels between the two groups. Note: Compared with before treatment, *P<0.05; compared with control group, #P<0.05.

*Liver function*

5 ml of venous blood was collected from patients before and after treatment, centrifuged at 3000 r/min for 10 min to separate the serum. Later, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured by rate method with HITACHI-7080 automatic biochemical analyzer (Hitachi, Japan); Total bilirubin (TBiL) was determined by vanadate oxidation method.

*Levels of myocardial injury indicators*

Venous blood was drawn from the patients before and after treatment. DuPont RXL automatic biochemical analyzer and supporting reagents were used to determine phosphocreatine kinase (CK) and creatine kinase isoenzyme (CPK-MB) levels.

Cardiovascular events including myocardial infarction, angina, heart failure, malignant arrhythmia, and all-cause deaths were recorded.

*Statistical analysis*

SPSS19.0 statistical software was adopted for data processing. The measurement data conforming to the normal distribution were expressed by mean ± standard deviation (mean ± SD), and compared by t test. Count data were expressed by ratio and examined by $\chi^2$ between groups. Rank sum test (Z test) was used for comparison of two groups of nonparametric (interval or not normally distributed) data, and P<0.05 was considered statistically significant.

## Results

*Baseline data comparison*

No significant difference was found between the two groups in gender, age, body mass index, smoking, drinking, consumption of statins and hepatoprotective drugs (all P> 0.05), which were comparable (**Table 1**).

*Comparison of clinical efficacy in both groups*

The efficacy of the OG was remarkably higher than that of the CG (P<0.05, **Table 2**).

*Comparison of blood lipid levels in both groups*

After treatment, the TC, TG, LDL-C of the both groups were remarkably reduced (P<0.05); In comparison with the CG, the above indicators in the OG improved more significantly after treatment (P<0.05); There was no significant change in HDL-C levels in both groups before and after treatment (P>0.05), suggesting that BSD can significantly improve the level of blood lipid in patients with NSTE ACSs and SEALs (**Figure 1**).

*Comparison of liver function indices in both groups*

After treatment, the ALT, AST and TBiL of both groups were significantly decreased (P<0.05);

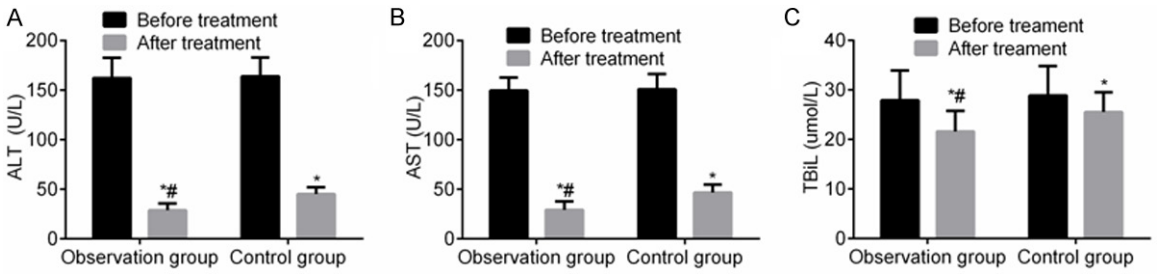


**Figure 2.** Comparison of liver function indexes between the two groups. Note: Compared with before treatment, *P<0.05; compared with control group, #P<0.05.

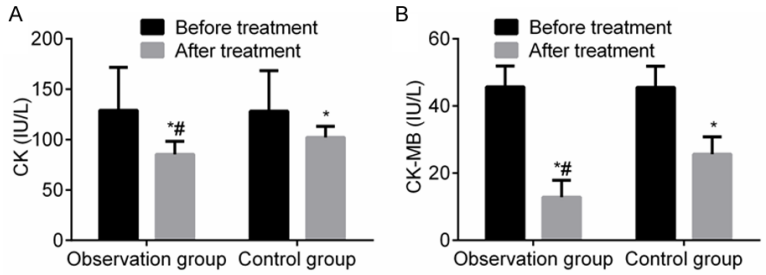


**Figure 3.** Comparison of myocardial injury indexes between the two groups. Note: Compared with before treatment, *P<0.05; compared with control group, #P<0.05.

these indicators were more remarkably reduced in the OG after treatment (P<0.05), suggesting that BSD can improve the liver function of patients (**Figure 2**).

*Comparison of myocardial injury indexes*

After treatment, CK and CK-MB in both groups were significantly reduced (P<0.05), which were more significantly decreased in the OG than in the CG (P<0.05), suggesting that BSD can improve the degree of myocardial damage in patients (**Figure 3**).

*Comparison of cardiovascular events*

The total incidence of cardiovascular events in the OG and CG were 9.62% (5/52) and 33.33% (17/51), respectively, and the OG was remarkably lower than the CG (P<0.05), suggesting that BAD can prevent the cardiovascular events (**Table 3**).

## Discussion

Non-ST-segment elevation ACS is one common type of ACS, mainly caused by incomplete occlusion of coronary arteries by atherosclerotic plaques. Clinically, intensive statin therapy aimed to regulate blood lipids, reduce inflammatory factors, and stabilize atherosclerotic plaques to prevent complications. The non-ST-segment elevation ACS needs stricter lipid-lowering requirements, and the LDL-C needs to be controlled below 1.8 mmol/L, or 30%-50% lower than the baseline. Therefore, in clinical practice, large doses of statins are used for the lipid-lowering therapy. As the dose of statins increases, the toxic and side effects towards liver and muscle gradually emerge. The liver damage caused by statins is dose-dependent [11, 12].

Studies found that the incidence of liver damage caused by statins is about 1.2/1 million, which is one specific form of liver disease [13, 14]. Although the liver damage caused by statin treatment has no obvious features, transaminases levels of the patients are elevated, which mostly occur within 3 months after the drug administration. Abnormal expression of ALT, AST, TBiL were found and further damage to liver function such as liver fibrosis and liver failure will also occur [15]. Therefore, most patients are forced to stop lipid-lowering treatment, which greatly increases the risk of MACE and is not conducive to patient prognosis.

NSTE ACS is a symptom of chest paralysis and heartache in Traditional Chinese medicine (TCM). Its main pathogenesis includes qi deficiency, blood stasis, phlegm turbidity, and stagnation, of which blood stasis and phlegm turbidity are the main causes. Thus, NSTE ACS should be treated by removing blood stasis and

**Table 3.** Comparison of the incidence of cardiovascular events between the two groups [n (%)]

| Group | n | Myocardial infarction | Angina pectoris | Heart failure | Malignant arrhythmia | All-cause death | Total incidence |
|---|---|---|---|---|---|---|---|
| Observation group | 52 | 0 (0.00) | 2 (3.85) | 2 (3.85) | 1 (1.92) | 0 | 9.62① |
| Control group | 51 | 1 (1.96) | 6 (11.76) | 5 (9.80) | 5 (9.80) | 0 | 33.33 |
| $\chi^2$ | - | - | - | - | - | - | 8.623 |
| *P* | - | - | - | - | - | - | 0.003 |

①Compared with control group, *P<0.05.*

turbidity [16]. It was believed in TCM that liver damage caused by statins was related to qi stagnation while the phlegm turbidity and blood stasis are further blocked in the liver, resulting in liver stagnation, meridian obstruction, and distortion of liver function. It will eventually lead to blockade of static blood, impaired meridians, and impaired liver function over time. Therefore, the treatment should be based on the principle of protecting liver and benefiting qi, activating blood circulation, and removing stasis as well as turbidity.

In view of the above pathogenesis, the OG was treated with a self-made BSD. BSD is a prescription in the treatment of acute coronary syndrome in our hospital. In the prescription, Astragalus invigorates spleen and replenishes qi; Codonopsis supplements the spleen and-nourishes the lungs, qi, and the blood; Angelica sinensis stagnates the blood and disperses blood stasis; Thorowax root relieves stagnation, nourishes Qi and protects the liver; Snakegourd fruit removes phlegm and dispels stasis; Szechuan lovage rhizome promotes blood circulation and relieves pain; Radix cyathulae promotes blood circulation; Both fructus aurantii and pinellia eliminate dampness and phlegm; Rehmannia glutinosa clears heat and cools blood, nourishes yin and regenerates blood; Safflower activates blood circulation, and relieves stasis and pain; Panax notoginseng powder disperses stasis. The whole prescription plays the function of protecting liver, benefiting qi and removing turbidity as well as blood stasis. Modern pharmacology found that astragalus has function of positive inotropic action and anti-heart failure, elimination of oxygen free radicals, regulation of blood pressure, expansion of coronary vessel, protection of toxic liver injury, etc. [17, 18]. Dangshen, danshen and angelica [19] play the role of regulating glucose and lipid metabolism. Thorowax root protects liver and gallbladder, lowers blood pressure, reduces fever and relieves the pain. The active ingredients of Szechwan Lovage Rhizome can dilate blood vessels and enhance the contractility of myocardium [20]. Snakegourd fruit, adix cyathulae [21], and fructus aurantii [22] could scavenge oxygen free radicals, dilate blood vessels, inhibit platelet aggregation and prevent thrombosis. To sum up, the self-made BSD can increase blood flow of coronary artery, improve blood supply of myocardium, enhance contractility of myocardium, and reduce the occurrence of cardiovascular events by dilating blood vessels, while astragalus and Thorowax root can effectively improve the liver function of patients.

The results of present study revealed that the total effective rate of the OG after treatment was higher than that of the CG, and TC, TG, LDL-C, ALT, AST, TBiL, CK, and CK-MB of the both groups were significantly reduced after treatment. These indices in the OG were improved more positively than in the CG, and the total incidence of cardiovascular events in the OG was remarkably lower, suggesting that the self-made SBD can significantly improve degree of myocardial damage, reduces blood lipid levels, improves liver function, and reduces the occurrence of cardiovascular events.

In conclusion, self-made BSD can significantly improve myocardial damage, effectively regulate blood lipid levels, improve liver function and reduce cardiovascular events in patients with NSTE ACS and SEALs.

## Disclosure of conflict of interest

None.

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## References


[1] Jobs A, Mehta SR, Montalescot G, Vicaut E, Van't Hof AWJ, Badings EA, Neumann FJ, Kastrati A, Sciahbasi A, Reuter PG, Lapostolle F, Milosevic A, Stankovic G, Milasinovic D, Vonthein R, Desch S and Thiele H. Optimal timing of an invasive strategy in patients with non-ST-elevation acute coronary syndrome: a meta-analysis of randomised trials. Lancet 2017; 390: 737-746.

[2] Anadol R, Dimitriadis Z, Polimeni A, Wendling F, Gönner S, Ullrich H, Lorenz L, Weissner M, Munzel T and Gori T. Bioresorbable everolimus-eluting vascular scaffold for patients presenting with non STelevation-acute coronary syndrome: a three-years follow-up1. Clin Hemorheol Microcirc 2018; 69: 3-8.

[3] Yu H, Ma L, Feng K, Chen H and Hu H. Clinical application of optical coherence tomography in patients with non-ST-elevation acute coronary syndrome combined with intermediate lesions. Heart Surg Forum 2017; 20: E032-E037.

[4] Chu CS, Tseng PT, Stubbs B, Chen TY, Tang CH, Li DJ, Yang WC, Chen YW, Wu CK, Veronese N, Carvalho AF, Fernandes BS, Herrmann N and Lin PY. Use of statins and the risk of dementia and mild cognitive impairment: a systematic review and meta-analysis. Sci Rep 2018; 8: 5804.

[5] Galappatthy P, Bataduwaarachchi VR, Ranasinghe P, Galappatthy GKS, Wijayabandara M, Warapitiya DS, Sivapathasundaram M, Wickramarathna T, Senarath U, Sridharan S, Wijeyaratne CN and Ekanayaka R. Management, characteristics and outcomes of patients with acute coronary syndrome in Sri Lanka. Heart 2018; 104: 1424-1431.

[6] Karahalil B, Hare E, Koç G, Uslu İ, Şentürk K and Özkan Y. Hepatotoxicity associated with statins. Arh Hig Rada Toksikol 2017; 68: 254-260.

[7] Lemesle G, Laine M, Pankert M, Puymirat E, Cuisset T, Boueri Z, Maillard L, Armero S, Cayla G, Bali L, Motreff P, Peyre JP, Paganelli F, Kerbaul F, Roch A, Michelet P, Baumstarck K and Bonello L. Early versus delayed invasive strategy for intermediate- and high-risk acute coronary syndromes managed without P2Y (12) receptor inhibitor pretreatment: design and rationale of the EARLY randomized trial. Clin Cardiol 2018; 41: 5-12.

[8] Emad M, Arjmand H, Farpour HR and Kardeh B. Lipid-lowering drugs (statins) and peripheral neuropathy. Electron Physician 2018; 10: 6527-6533.

[9] Niu X, Liu G, Huo L, Zhang J, Bai M, Peng Y and Zhang Z. Risk stratification based on components of the complete blood count in patients with acute coronary syndrome: a classification and regression tree analysis. Sci Rep 2018; 8: 2838.

[10] Cho YM, Kwon JE, Lee M, Lea Y, Jeon DY, Kim HJ and Kang SC. Agrimonia eupatoria L. (Agrimony) Extract alters liver health in subjects with elevated alanine transaminase levels: a controlled, randomized, and double-blind trial. J Med Food 2018; 21: 282-288.

[11] Alquézar A, Santaló M, Rizzi M, Gich I, Grau M, Sionis A and Ordóñez-Llanos J. Combined high-sensitivity copeptin and troponin T evaluation for the diagnosis of non-ST elevation acute coronary syndrome in the emergency department. Emergencias 2017; 29: 237-244.

[12] Naiqiong W, Liansheng W, Zhanying H, Yuanlin G, Chenggang Z, Ying G, Qian D, Dongchen L, Yanjun Z and Jianjun L. A Multicenter and randomized controlled trial of bicyclol in the treatment of statin-induced liver injury. Med Sci Monit 2017; 23: 5760-5766.

[13] Ganyukov VI, Tarasov RS, Neverova YN, Kochergin NA, Barbarash OL and Barbarash LS. Long-term results of different approaches to revascularization in non-ST-segment elevation acute coronary syndrome and multiple coronary atherosclerosis. Ter Arkh 2017; 89: 29-34.

[14] Kashef MA and Giugliano G. Legacy effect of statins: 20-year follow up of the West of Scotland Coronary Prevention Study (WOSCOPS). Glob Cardiol Sci Pract 2016; 2016: e201635.

[15] McWilliam SJ, Antoine DJ and Pirmohamed M. Repurposing statins for renal protection: is it a class effect? Clin Transl Sci 2018; 11: 100-102.

[16] Ma A, Tao T and Wu Z. Changes of contents of serum ICAM-1, VCAM-1, CD40L and their relationship with TCM syndrome types in patients with acute coronary syndrome. Modern Journal of Integrated Traditional Chinese & Western Medicine 2017.

[17] Kim H, Lee H, Kim TM, Yang SJ, Baik SY, Lee SH, Cho JH, Lee H, Yim HW, Choi IY, Yoon KH and Kim HS. Change in ALT levels after administration of HMG-CoA reductase inhibitors to subjects with pretreatment levels three times the upper normal limit in clinical practice. Cardiovasc Ther 2018; 36: e12324.

[18] Du JP, Wang CL, Wang PL, Wang SL, Gao ZY, Zhang DW, Xu H and Shi DZ. Efficacy of Chinese herbs for supplementing Qi and activating blood circulation on patients with acute coronary syndrome and type 2 diabetes mellitus after percutaneous coronary intervention: a clinical observation. Zhongguo Zhong Xi Yi Jie He Za Zhi 2015; 35: 563-567.

[19] Guan Z, Chen X, Song G, Yu S, Zhang Y and Lv W. Clinical efficacy of Xiaoxianxiong decoction and Danshen decoction in treating patients

with phlegm-heat interconnected viral myocarditis and its effects on immune function and oxygen free radicals. World Chinese Medicine 2019; 14: 154-158.

[20] Hou M, Zhang Y, Zheng S and Qiao Y. Mechanism of tetramethylpyrazine in treatment of coronary heart disease based on the coexpression-protein interaction network. Journal of Beijing University of Chinese Medicine 2016; 39: 989-997.

[21] Yang YH, Li MJ, Yi YJ, Li RF, Dong C and Zhang ZY. The root transcriptome of Achyranthes bidentata and the identification of the genes involved in the replanting benefit. Plant Cell Rep 2018; 37: 611-625.

[22] Li L, Zhang S, Xin Y, Sun J, Xie F, Yang L, Chen Z, Chen H, Liu F, Xuan Y and You Z. Role of Quzhou fructus aurantii extract in preventing and treating acute lung injury and inflammation. Sci Rep 2018; 8: 1698.