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Original Article

The feasibility of using Hcy, CRP, and Cys-C to analyze AMI patients' disease conditions and prognoses

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Abstract: Objective: This study was conducted to investigate the feasibility of using the serum homocysteine (Hcy), C-reactive protein (CRP), and cystatin C (Cys-C) levels to evaluate the conditions and prognoses of acute myocardial infarction (AMI) patients. Methods: One hundred and twenty patients with AMI were enrolled as an observation group (the AMI group). Eighty patients with stable angina pectoris were included in a control group (the SA group). Eighty healthy volunteers were enrolled as a healthy control group (the NCHD group). The AMI patients were divided into groups of >20 (n = 32), 10-20 (n = 45) and <10 (n = 43) according to their APACHE-II scores. The groups were divided into a death group (n = 23) and a survival group (n = 97) according to the patients' 1-year follow-up outcomes. The differences in the serum Hcy, CRP, and Cys-C levels among the different groups, and the correlations between the serum levels were calculated. Results: The serum Hcy, CRP, and Cys-C levels in the AMI group were significantly higher than they were in the SA and NCHD groups (P<0.05), and the serum levels in the APACHE-II score >20 group were significantly higher than the serum levels in the 10-20 group. The dead group exhibited higher serum Hcy, CRP, and Cys-C levels than the survival group (P<0.05), and our Spearman's correlation analysis showed that the serum Hcy, CRP and Cys-C levels were positively correlated with the APACHE II scores (r = 0.9157, r = 0.8519, r = 0.8598, P<0.001). The area under curve of Hcy, CRP, and Cys-C for the AMI diagnoses were 0.9638 (95% CI: 0.9183-1.000), 0.8125 (95% CI: 0.6652-0.9598), and 0.7515 (95% CI: 0.5847-0.9184), respectively. Conclusion: Serum Hcy, CRP, and Cys-C levels can reflect the severity of the patients' conditions.

Keywords: Hcy, CRP, Cys-C, disease prognosis, analysis, feasibility investigation

Introduction

With the development of the domestic economy, residents' dietary habits and lifestyles have undergone great changes. The incidence rate of cardiovascular diseases has increased significantly. Acute myocardial infarction (AMI) is a kind of myocardial necrosis caused by acute or persistent coronary ischemia and hypoxia [1]. Patients with AMI usually have severe and long-lasting retrosternal pain that can be appropriately relieved with rest or nitrate drugs. Clinical trials show increased myocardial enzyme activity and progressive ECG changes [2, 3]. Some patients may experience arrhythmia, shock, or heart failure, which may threaten patients' lives and health. Data show that AMI is currently the leading cause of death worldwide. There are 500,000 AMI cases each year in China, and its mortality rate has ranked first since 2014 [4, 5].

Clinical practice has found that patients with AMI in critical condition often suffer from myocardial necrotizing disease due to continuous severe ischemia and hypoxia. Most patients have poor prognosis due to impaired cardiac function, and some patients have a higher chance of sudden death or recurrence. At the same time, due to the rapid development of AMI, it is clinically recommended to carry out active monitoring and prognostic analysis for patients, followed by targeted interventions to reduce the recurrence and mortality [6, 7].

Hcy is an important metabolic intermediate in the human body, and it is also a diagnostic index for cardiovascular disease. A study has found that Hcy levels can be used as an independent risk factor for atherosclerosis, and when an individual's serum Hcy level increases by 5 μmol/L, the risk of stroke increases by 59% [8]. CRP is a non-specific inflammation

marker, and the CRP level is dramatically increased when an individual is exposed to infection or tissue damage. Clinical practice has shown that CRP is directly involved in inflammation and cardiovascular diseases such as atherosclerosis and is the strongest predictor and risk factor for cardiovascular disease [9]. Cys-C, a protein encoded by the CST3 gene, is clinically used as a biomarker of renal function, but recent studies have indicated that Cys-C is also useful in predicting the occurrence or worsening of cardiovascular disease [10, 11]. The present study was conducted to investigate the application value of the above serum indices in the diagnosis and prognosis analysis of AMI patients, so as to provide a clinical reference for relieving the clinical symptoms of AMI patients.

Materials and methods

General information

One hundred and twenty patients with AMI treated in the Affiliated Hospital of Chengde Medical University from January 2016 to January 2019 were placed in the observation group (the AMI group). Another 80 patients with stable angina treated in our hospital during the same period were enrolled as the case control group (the SA group), and 80 healthy individuals were placed in the healthy control group (the NCHD group).

Inclusion criteria: (1) The patients in the AMI group all met the AMI diagnostic criteria [12], (2) Patients with a clear consciousness and good compliance, (3) Patients with complete medical records, and (4) Patients ≤70 years old. The present study was approved by the hospital ethics committee. The patients or their families signed the informed consent form.

Exclusion criteria: (1) Patients with psychiatric disorders, (2) Patients with other serious underlying physical disorders, (3) Patients with uncontrolled cardiac arrhythmia, (4) Patients with decompensated heart failure, (5) Patients with poor treatment compliance, (6) Patients with malignant tumors, (7) Patients with severe hepatic or renal insufficiency, (8) Patients with autoimmune diseases, (9) Pregnant or lactating women, and (10) Patients with hematologic disorders or chronic gastrointestinal disorders that may affect their serum factor levels.

Withdrawal criteria: (1) Patients who developed diseases or illnesses that interfered with the results, (2) Patients who voluntarily withdrew during the study, (3) Patients who lost contact with the research team.

Intervention method

Blood sample collection and testing: All the subjects were instructed to fast from 22:00, and 5 ml of peripheral elbow vein blood was drawn from each at 6:00-7:00 a.m. the next morning. The samples were treated with anticoagulant (heparin anticoagulation) and left for 30 min, followed by centrifugation at 3000 r/min for 15 min. The upper plasma was poured into heparin anticoagulant tubes, and stored at -80°C. The Hcy, CRP, and Cys-C levels were measured using enzyme-linked immunosorbent assays (ELISA), and all the kits used were purchased from Siemens AG. The measurement procedures were carried out strictly in accordance with the kits' instructions. The average value of each index was taken as the final result after three consecutive tests.

Grouping of the patients: The APACHE II score is a general measure of disease severity based on current physiologic measurements, age and previous health conditions. APACHE II score = acute physiology score + age points + chronic health points. Minimum score = 0; maximum score = 71. Increased scores are associated with an increased risk of hospital death. According to their APACHE II scores, 120 patients in the AMI group were divided into the score of >20 group (n = 32), the 10-20 group (n = 45) and the <10 group (n = 43). After a 1-year follow-up, the patients were divided into death (n = 23) and survival groups (n = 97) according to their clinical outcomes.

Observation indicators

Comparison of the differences in the serological parameters: The serum Hcy, CRP, and Cys-C levels were compared among the patients in the AMI, SA, and NCHD groups, among the APACHE II score of >20, 10-20, and <10 groups, and between the death and survival groups.

Correlation between the serological parameters and the APACHE II scores: Spearman's correlation analysis was used to investigate the relationship between the serologic parameters and the APACHE II scores.

Table 1. Comparison of the baseline data ($\bar{x} \pm s$)/[n (%)]

Clinical information		AMI Group (n = 120)	SA group (n = 80)	NCHD group (n = 80)	*F*	*P*
Gender	Male	71	45	50	0.547	0.362
	Female	49	35	30		
Average age (years)		44.59±3.22	45.19±2.98	44.28±3.01	0.036	0.987
Average weight (kg)		63.29±3.41	64.11±2.98	64.33±3.22	0.066	0.917
History of hypertension	Yes	20	13	15	0.445	0.298
	No	100	67	65		
History of diabetes	Yes	23	15	10	0.591	0.322
	No	97	65	70		

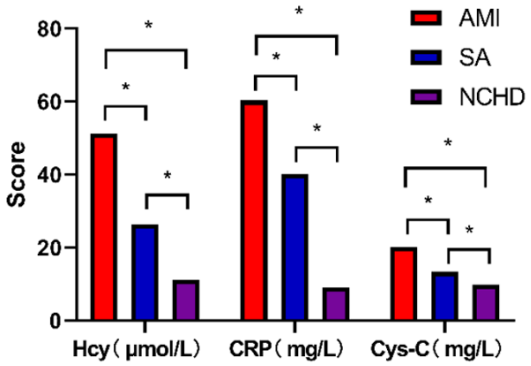

Figure 1. Comparison of the serological indexes among the AMI, SA, and NCHD groups. The Hcy, CRP, and Cys-C levels in the AMI group were significantly higher than the corresponding levels in the SA and NCHD groups ($P<0.05$), and the above indices in the SA group were significantly higher than they were in the NCHD group. * represents a significant difference of the same index between groups, $P<0.05$.

The value of the serological indices for the diagnosis of AMI: The ROC curves of the serum Hcy, CRP, and Cys-C levels for the diagnosis of AMI were each drawn, and the areas under the curves (AUC) for Hcy, CRP, and Cys-C were calculated, and the diagnostic values of Hcy, CRP, and Cys-C for AMI were analyzed.

Statistical methods

SPSS 22.0 was used for the data analysis. If the data conformed to a normal distribution, the count data were expressed as [n (%)], and the differences between groups were examined using *Chi*-square tests, while the measurement data were expressed as the (mean ± standard deviation) and compared using t tests. F tests were used to compare the differences among multiple groups, and Spearman rank correlation coefficient was used for the correlation analysis. $P<0.05$ was considered statistically significant [13].

Results

Comparison of the differences in the baseline data

There were no significant differences among the three groups in terms of their gender ratios, mean ages, mean weights, or underlying diseases ($P>0.05$), so they were comparable (**Table 1**).

Comparison of the serological parameters of the patients in the AMI, SA, and NCHD groups

There were significant differences in the levels of the serological indices among the three groups ($P<0.05$). The Hcy, CRP, and Cys-C levels in the AMI group were higher than the corresponding levels in the SA and NCHD groups ($P<0.05$), and the levels of the above indices in the SA group were higher than they were in the NCHD group ($P<0.05$) (**Figure 1**).

Comparison of the serological parameters in patients with different APACHE II scores

The patients' Hcy, CRP, and Cys-C levels in the APACHE II score >20 group were significantly higher than those of the patients in the 10-20 and <10 groups, but the patients in the 10-20 group had higher levels of the above indices than the patients in the <10 group ($P<0.05$) (**Figure 2**).

Comparison of the serological parameters in the patients with different clinical outcomes

The patients in the death group had significantly higher Hcy, CRP, and Cys-C levels than the patients in the survival group ($P<0.05$) (**Figure 3**).

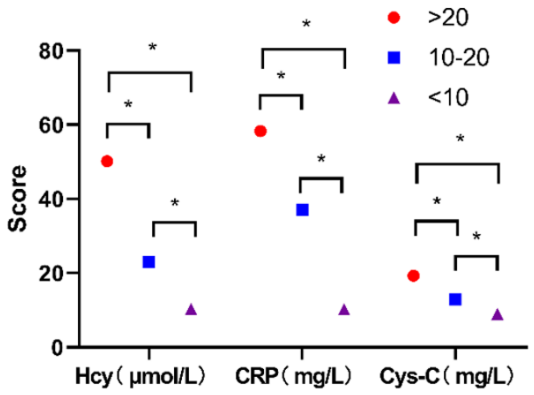

Figure 2. Comparison of the differences in the serological indices among the patients with different APACHE II scores. The Hcy, CRP, and Cys-C levels in the APACHE II >20 group were significantly higher than they were in the 10-20 and <10 groups, and the Hcy, CRP, and Cys-C levels in the 10-20 group were significantly higher than they were in the <10 group. * represents a significant difference in the same index between groups, $P<0.05$.

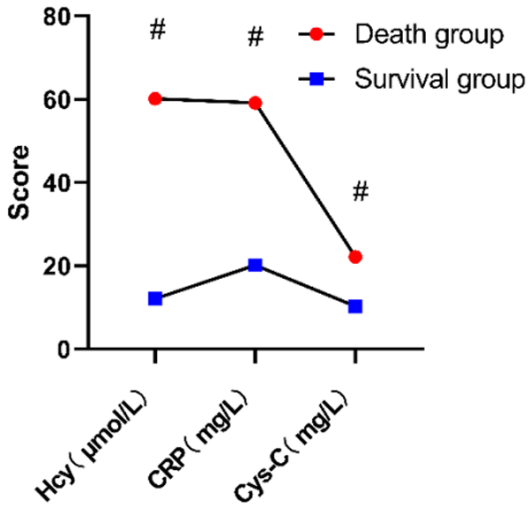

Figure 3. Comparison of the differences in the serological parameters among the patients with different clinical outcomes. The Hcy, CRP, and Cys-C levels in the death group were significantly higher than the corresponding levels in the survival group. # represents a significant difference in the same index between groups, $P<0.05$.

Correlation analysis of the serological parameters with the APACHE II scores

A significant positive relationship was found between the Hcy, CRP, and Cys-C levels and the APACHE II scores (r = 0.9157, r = 0.8519, r = 0.8598, $P<0.001$) (**Figure 4**).

The value of the serological indices in the diagnosis of AMI

The AUCs of Hcy, CRP and Cys-C for the diagnosis of AMI were 0.9638, 0.8125, and 0.7515, and the 95% CI were 0.9183-1.000, 0.6652-0.9598, and 0.5847-0.9184, respectively ($P<0.05$), suggesting that the above indicators have a high value in the diagnosis of AMI (**Figure 5**).

The sensitivity of the serological parameters for the diagnosis of AMI

The sensitivity, specificity, and accuracy of the serum Hcy, CRP, and Cys-C levels for the diagnosis of AMI were 89.28%, 78.89%, 73.22%, 91.72%, 78.28%, 70.77%, 90.17%, 67.67%, and 87.12%, respectively, with only small differences among the groups ($P>0.05$) (**Table 2**).

Discussion

AMI is a serious cardiovascular disease with a high mortality rate. Under the influence of lifestyles, social aging, and changes in dietary structure, the prevalence of AMI is on the rise worldwide, posing a serious threat to human health [14, 15]. Due to the rapid onset and poor prognosis of AMI, most patients will still have adverse consequences such as reduced cardiopulmonary function, decreased exercise tolerance, as well as self-care ability after timely interventions. Therefore, appropriate interventions are recommended to improve the patients' quality of life [16].

In this study, the differences in the serum Hcy, CRP, and Cys-C levels in AMI patients with different courses of the disease and different prognoses were explored by setting up different groups. The results showed that the Hcy, CRP and Cys-C levels in the SA group were significantly higher than the corresponding levels in the NCHD group, suggesting that with the aggravation of the disease condition, the serum factor levels of the patients showed significant changes. A comparative study of 66 AMI patients showed that the serum Hcy, hs-CRP and Cys-C levels of AMI patients were significantly higher than the levels in healthy individuals, and these levels showed a positive correlation with each other, suggesting that they can be used in the assessment of AMI patients' conditions [17]. The current monitoring mea-

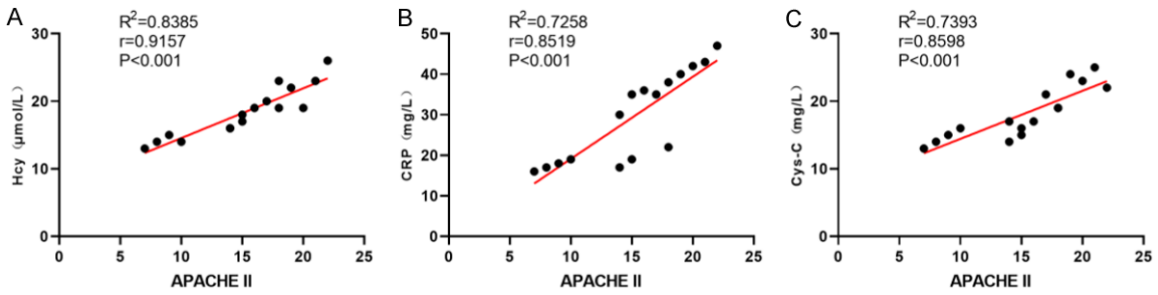

Figure 4. A correlation analysis of the serological parameters with the APACHE II scores. The Hcy (A), CRP (B), and Cys-C (C) levels showed significant positive associations with the APACHE II scores (r = 0.9157, r = 0.8519, r = 0.8598, *P*<0.001).

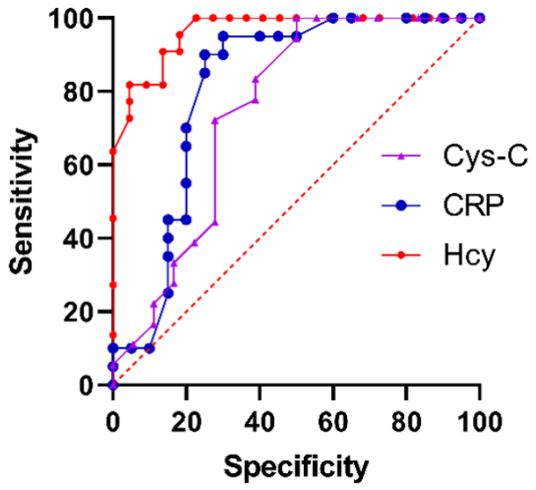

Figure 5. The value of the serological parameters for diagnosing AMI. The AUCs of Hcy, CRP, and Cys-C for diagnosing AMI were 0.9638, 0.8125, and 0.7515, and the 95% CIs were 0.9183-1.000, 0.6652-0.9598, and 0.5847-0.9184, respectively (*P*<0.05).

Table 2. Analysis of the sensitivity, specificity and accuracy

Indices	Sensitivity	Specificity	Accuracy
Hcy	89.28%	78.89%	73.22%
CRP	91.72%	78.28%	70.77%
Cys-C	90.17%	67.67%	87.12%
F	1.221	0.989	0.782
P	>0.01	>0.05	>0.05

sures for AMI mainly rely on ECG, laboratory tests, *etc*. Among them, the interpretation of the ECG results depends on the physicians' experience, and the cardiac dysfunction may lead to large errors in the ECG results, so it is not recommended to use ECG as the only means of diagnosing and identifying AMI [18, 19]. Laboratory tests have the advantages of speed, good repeatability, and high accuracy, and they are also commonly used in clinical practice. Hcy is a reactive vascular injury amino acid and one of the important metabolic intermediates of the human body. The abnormal elevation of Hcy is closely associated with the occurrence of cardiovascular diseases, which have been clinically regarded as an independent risk factor for atherosclerotic lesions [20]. The mechanisms of Hcy that have been demonstrated as an independent risk factor for cardiovascular disease may be as follows: (1) Hcy promotes the generation of oxygen free radicals , and its elevated level will damage vascular endothelial cells, (2) Hcy can affect the process of apoptosis in vascular endothelial cells and inhibit the growth of vascular endothelial cells, (3) Hcy can regulate the body's lipid metabolism and promote lipid peroxidation, which in turn accelerates the oxidation of LDL, (4) Hcy accelerates platelet aggregation and adhesion and induces thrombosis [21]. CRP is an acute phase response protein synthesized by hepatocytes, mostly present in the form of glycoprotein in the blood. CRP levels are extremely low in healthy people but can rise sharply when an individual has an infection or tissue damage. The abnormal elevation of serum CRP levels may be related to cardiovascular rupture, and a study has found that CRP levels are positively correlated with the incidence of sudden cardiac death [22]. CRP has been confirmed to be closely related to individual tissue damage and inflammation. AMI is characterized by cell apoptosis which will stimulate the body to secrete a large amount of CRP. Therefore, the CRP level is closely related to the disease condition, so it is also evidenced in the index differences among patients with different APACHE II scores. It has been demonstrated that Cys-C participates in the homeo-

stasis of extracellular matrix production and degradation by regulating the protease activity of Hcy. Cys-C can also affect cellular phagocytosis and chemotaxis, so it is involved in the inflammatory process, and this has also been demonstrated by the differences in serum blood parameters among AMI patients with varying disease stages [23, 24].

Hcy, CRP, and Cys-C levels are positively associated with the APACHE II scale scores. A retrospective study on AMI patients showed that the BNP, Hcy, and hs-CRP levels in AMI patients were significantly correlated with the disease condition and could be considered indicators for the assessment of the conditions of AMI patients, and the results also showed that the Hcy, cTnT, and PCT levels were correlated with the prognostic index scores (SIRS) of AMI patients, which confirms the association between the serological indicators and the prognosis [25]. The AUCs of Hcy, CRP, and Cys-C for the diagnosis of AMI were 0.9638, 0.8125, and 0.7515 respectively, indicating that the serological indices have a good diagnostic value for AMI. A study pointed out that the more severe the inflammatory response in the initial stage of AMI patients, the longer the duration of the disease, and the greater the possibility of later worsening. The higher the level of Hcy, the worse the patient's prognosis and the higher the probability of stroke and myocardial infarction [26].

In summary, the serum Hcy, CRP, and Cys-C levels are valuable for assessing AMI patients' conditions and prognoses and indicating the severity of the patients' conditions. However, the small sample size and the short-term follow-up may still limit the accuracy of the experimental results, and further large-scale prospective studies are yet to be carried out.

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Disclosure of conflict of interest

None.

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References

[1] Anderson JL and Morrow DA. Acute myocardial infarction. N Engl J Med 2017; 376: 2053-2064.

[2] Thiele H, Akin I, Sandri M, Fuernau G, de Waha S, Meyer-Saraei R, Nordbeck P, Geisler T, Landmesser U, Skurk C, Fach A, Lapp H, Piek JJ, Noc M, Goslar T, Felix SB, Maier LS, Stepinska J, Oldroyd K, Serpytis P, Montalescot G, Barthelemy O, Huber K, Windecker S, Savonitto S, Torremante P, Vrints C, Schneider S, Desch S and Zeymer U. PCI strategies in patients with acute myocardial infarction and cardiogenic shock. N Engl J Med 2017; 377: 2419-2432.

[3] Wongcharoen W, Sutthiwutthichai S, Gunaparn S and Phrommintikul A. Is non-HDL-cholesterol a better predictor of long-term outcome in patients after acute myocardial infarction compared to LDL-cholesterol? A retrospective study. BMC Cardiovasc Disord 2017; 17: 10.

[4] Cafagna G and Seghieri C. Educational level and 30-day outcomes after hospitalization for acute myocardial infarction in Italy. BMC Health Serv Res 2017; 17: 18.

[5] Smolderen KG, Spertus JA, Gosch K, Dreyer RP, D'Onofrio G, Lichtman JH, Geda M, Beltrame J, Safdar B, Bueno H and Krumholz HM. Depression treatment and health status outcomes in young patients with acute myocardial infarction: insights from the VIRGO study (variation in recovery: role of gender on outcomes of young AMI patients). Circulation 2017; 135: 1762-1764.

[6] Krumholz HM, Hennen J, Ridker PM, Murillo JE, Wang Y, Vaccarino V, Ellerbeck EF and Radford MJ. Use and effectiveness of intravenous heparin therapy for treatment of acute myocardial infarction in the elderly. J Am Coll Cardiol 1998; 31: 973-979.

[7] Lellouche F, Simon M and L'Her E. Oxygen therapy in suspected acute myocardial infarction. N Engl J Med 2018; 378: 201.

[8] Hofmann R, Svensson L and James SK. Oxygen therapy in suspected acute myocardial infarction. N Engl J Med 2018; 378: 201-202.

[9] Mohammadi R, Khodakarim S, Alipour A, Bitaraf E and Soori H. Association between air temperature and acute myocardial infarction hospitalizations in Tehran, Iran: a time-stratified case-crossover. Int J Occup Environ Med 2017; 8: 143-152.

[10] Tung YC, Chang GM, Chang HY and Yu TH. Relationship between early physician follow-up and 30-day readmission after acute myocardi-

al infarction and heart failure. PLoS One 2017; 12: e0170061.
[11] Al-Lamee R, Thompson D, Dehbi HM, Sen S, Tang K, Davies J, Keeble T, Mielewczik M, Kaprielian R, Malik IS, Nijjer SS, Petraco R, Cook C, Ahmad Y, Howard J, Baker C, Sharp A, Gerber R, Talwar S, Assomull R, Mayet J, Wensel R, Collier D, Shun-Shin M, Thom SA, Davies JE and Francis DP. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. Lancet 2018; 391: 31-40.
[12] Lassen JF, Burzotta F, Banning AP, Lefèvre T, Darremont O, Hildick-Smith D, Chieffo A, Pan M, Holm NR, Louvard Y and Stankovic G. Percutaneous coronary intervention for the left main stem and other bifurcation lesions: 12th consensus document from the European Bifurcation Club. EuroIntervention 2018; 13: 1540-1553.
[13] Metz L, Thivel D, Peirrera B, Richard R, Julian V and Duclos M. A new equation based on the 6-min walking test to predict VO(2peak) in women with obesity. Disabil Rehabil 2018; 40: 1702-1707.
[14] Zannad F and Ferreira JP. Reply: cardiopulmonary exercise testing versus 6-min walk test as clinically meaningful endpoints in HF trials. J Am Coll Cardiol 2017; 69: 2252.
[15] Wang Z, Wang L, Su X, Pu J, Jiang M and He B. Rational transplant timing and dose of mesenchymal stromal cells in patients with acute myocardial infarction: a meta-analysis of randomized controlled trials. Stem Cell Res Ther 2017; 8: 21.
[16] Gao L, Liu Y, Guo S, Yao R, Wu L, Xiao L, Wang Z, Liu Y and Zhang Y. Circulating long noncoding RNA HOTAIR is an essential mediator of acute myocardial infarction. Cell Physiol Biochem 2017; 44: 1497-1508.
[17] Psotka MA, Schiller NB, Whooley MA and Mishra RK. Association of change in 5-year N-terminal fragment of the prohormone brain-type natriuretic peptide with left ventricular structure and function in stable coronary disease. J Cardiovasc Med (Hagerstown) 2018; 19: 67-72.
[18] Ambavane A, Lindahl B, Giannitsis E, Roiz J, Mendivil J, Frankenstein L, Body R, Christ M, Bingisser R, Alquezar A and Mueller C. Correction: economic evaluation of the one-hour rule-out and rule-in algorithm for acute myocardial infarction using the high-sensitivity cardiac troponin T assay in the emergency department. PLoS One 2018; 13: e0191348.
[19] Burzotta F, Lassen JF, Banning AP, Lefèvre T, Hildick-Smith D, Chieffo A, Darremont O, Pan M, Chatzizisis YS, Albiero R, Louvard Y and Stankovic G. Percutaneous coronary intervention in left main coronary artery disease: the 13th consensus document from the European Bifurcation Club. EuroIntervention 2018; 14: 112-120.
[20] Lindholm D, Alfredsson J, Angerås O, Böhm F, Calais F, Koul S, Lagerqvist B, Renlund H, Sarno G and Varenhorst C. Timing of percutaneous coronary intervention in patients with non-ST-elevation myocardial infarction: a SWEDEHEART study. Eur Heart J Qual Care Clin Outcomes 2017; 3: 53-60.
[21] Poder TG, Erraji J, Coulibaly LP and Koffi K. Percutaneous coronary intervention with second-generation drug-eluting stent versus bare-metal stent: systematic review and cost-benefit analysis. PLoS One 2017; 12: e0177476.
[22] Papapostolou S, Andrianopoulos N, Duffy SJ, Brennan AL, Ajani AE, Clark DJ, Reid CM, Freeman M, Sebastian M, Selkrig L, Yudi MB, Noaman SQ and Chan W. Long-term clinical outcomes of transient and persistent no-reflow following percutaneous coronary intervention (PCI): a multicentre Australian registry. EuroIntervention 2018; 14: 185-193.
[23] Yan W, Li RJ, Jia Q, Mu Y, Liu CL and He KL. Neutrophil-to-lymphocyte ratio compared to N-terminal pro-brain natriuretic peptide as a prognostic marker of adverse events in elderly patients with chronic heart failure. J Geriatr Cardiol 2017; 14: 127-134.
[24] Khan A, Phadke M, Lokhandwala YY and Nathani PJ. A study of prehospital delay patterns in acute myocardial infarction in an urban tertiary care institute in Mumbai. J Assoc Physicians India 2017; 65: 24-27.
[25] Bourron O, Le Bouc Y, Berard L, Kotti S, Brunel N, Ritz B, Leclercq F, Tabone X, Drouet E, Mulak G, Danchin N and Simon T. Impact of age-adjusted insulin-like growth factor 1 on major cardiovascular events after acute myocardial infarction: results from the fast-MI registry. J Clin Endocrinol Metab 2015; 100: 1879-1886.
[26] Westermann C, Wendeler D and Nienhaus A. Hepatitis C in healthcare personnel: secondary data analysis of therapies with direct-acting antiviral agents. J Occup Med Toxicol 2018; 13: 16.