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Original Article

The value of Copeptin, myocardial fatty acid-binding protein and myocardial markers in the early diagnosis of acute myocardial infarction

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Abstract: Objective: To evaluate and detect the value of Copeptin, myocardial fatty acid binding protein (H-FABP) and myocardial markers in the early diagnosis of acute myocardial infarction (AMI). Method: A retrospective analysis was carried out in 153 patients with chest pain who came to Xianyang Hospital of Yan'an University from August 2019 to April 2022, of whom 87 patients were finally diagnosed with AMI. Cardiac troponin I (cTnI), Copeptin, and H-FABP levels were measured immediately at the patient's visit. Receiver operating characteristic (ROC) curve was drawn to evaluate and compare the value of Copeptin, H-FABP and cTnI in early diagnosis of AMI and their joint effect in improving the accuracy of early diagnosis of AMI. Results: (1) The levels of Copeptin, H-FABP and cTnI in AMI patients were evidently higher than those in non-AMI patients with chest pain. (2) The diagnostic sensitivity and specificity of Copeptin were 82.89% and 64.37%, respectively. Those of cTnI were 78.95% and 64.37% respectively, and those of H-FABP were 85.53% and 75.86%, respectively. The AUC size under the ROC curve was H-FABP > hopeptin > cTnI. (3) Joint detection of Copeptin, H-FABP and cTnI was better than mono-detection in early diagnosis of AMI. Conclusion: H-FABP has high accuracy in detecting early AMI, which is better than cTnI and Copeptin, but the joint detection of the three is of the highest value.

Keywords: Copeptin, cardiac fatty acid-binding protein, cardiac troponin I, acute myocardial infarction, early diagnosis

Introduction

Acute myocardial infarction (AMI) is a severe and persistent acute myocardial ischemia resulting in myocardial necrosis caused by a sharp reduction or interruption of coronary blood supply on the basis of coronary artery disease [1]. The first clinical symptoms are chest tightness and chest pain. If not treated in time, it will lead to disability and death due to its rapid progress, which seriously poses a threat to the life and safety of patients [2]. Fortunately, the mortality rate can be effectively reduced if rescue can be carried out in due course, for which the first 4-6 hours after myocardial infarction is the golden period [3]. In the early clinical diagnosis of AMI, electrocardiogram examination and clinical symptoms are often used as the diagnostic criteria. However, most AMI patients have no obvious clinical symptoms or obvious electrocardiographic changes in the early onset, resulting in missed diagnosis or misdiagnosis [4, 5]. Another gold standard for early clinical diagnosis of AMI, coronary angiography, is limited in its clinical application due to its long detection cycle and invasiveness [6]. Therefore, it is of great significance to find a diagnostic method with high safety, less trauma and corresponding diagnostic value in clinical diagnosis.

Cardiac troponin I (cTnI) is a routine myocardial marker for diagnosing AMI in clinical practice, which is of great significance for maintaining the diastolic and contractile ability of the heart. After the onset of the disease, cardiomyocytes are damaged and cTnI enters into the blood, but it appears in the blood in the middle and late term of diagnosis, causing low sensitivity for early AMI diagnosis [7]. In recent years, cardiac fatty acid-binding protein (H-FABP) has been found widely distributed in the cytoplasm of various organs of the body, which is of great significance in regulating the absorption and

metabolism of long-chain fatty acids [8]. Copeptin, a newly discovered marker of myocardial necrosis, has been listed as one of the most potential cardiac markers by the National Society of Clinical Biochemistry in the United States [9]. Generally speaking, single indicator detection has certain limitations, and the accuracy of combined diagnosis is normally higher. Although the above indicators can be used as diagnostic markers for acute myocardial infarction, the comparison of their diagnostic value and the value of combined diagnosis have not been reported.

In this study, we discussed the value of Copeptin, cardiac troponin I (cTnI) and H-FABP in the early diagnosis of acute myocardial infarction, so as to provide a more accurate reference index and basis for the diagnosis of early acute myocardial infarction.

Materials and methods

Clinical information

A retrospective analysis was carried out on 153 patients (81 male and 73 female) with chest pain who came to Xianyang Hospital of Yan'an University from August 2019 to April 2022, of whom 87 patients were finally diagnosed with AMI and were collected as the AMI Group (the diagnosis was confirmed by electrocardiogram, chest X-ray, CT and myocardial enzyme indexes after admission), and the remaining 76 were seen as the control group (differentially diagnosed as pulmonary embolism, aortic dissection, myocarditis, etc.).

Inclusion criteria: (1) in line with the diagnostic criteria of AMI [10]; (2) aged ≥ 18 years; (3) complete clinical data.

Exclusion criteria: (1) severe heart disease; (2) dysfunction of important organs such as liver and kidney; (3) severe infectious diseases and immune dysfunction; (4) malignant tumors; (5) refusal to participate. This study obtained approval from Xianyang Hospital of Yan'an University ethics committee (No. 20190745) and complies with the Helsinki Declaration.

Detection method

Two ml of venous blood were collected from both groups of subjects on admission (within 3 hours of onset), centrifuged at 4000 r/min for 5 min, and then the supernatant was separated and stored accordingly for testing. (1) H-FABP level was detected by Abbott C8000 automatic biochemical analyzer using immunoturbidimetric method; (2) Copeptin was detected by ELISA method (all reagents adopted were from Abcam Company, ab289701); (3) cTnI level was detected by electrochemiluminescence using an automatic immunoassay analyzer (Roche, Switzerland; Cobas E601). All operations were carried out in strict accordance with the kit instructions.

Coronary artery lesion assessment

All selected patients underwent coronary angiography (CAG) 7 days to 14 days after admission, and CAG was completed by experienced interventional cardiologists, using standard Judkin method. At least 3 multi-position projections were performed in each vessel.

Observation indicators

(1) The serum H-FABP, Copeptin and cTnI levels of the two groups of patients were detected and compared. (2) Serum H-FABP, Copeptin and cTnI were compared in patients with different degrees of coronary artery disease. (3) The diagnostic value of serum H-FABP, Copeptin and cTnI in early acute myocardial infarction were analyzed. (4) The combined diagnostic value of serum H-FABP, Copeptin and cTnI for early acute myocardial infarction was analyzed.

Statistical methods

SPSS 20.0 was used for statistical analysis of collected data, and GraphPad Prism 8 was for figure rendering. Chi-square test was for comparison of count data. For measurement data, the inter-group comparison and intra-group comparison were conducted with Student-t test and Paired-t test respectively, denoted by t. One-way ANOVA was for comparison among multiple groups, and LSD-t test for post-hoc test. The receiver operating curve (ROC) was used to analyze the diagnostic value of H-FABP, Copeptin and cTnI in early acute myocardial infarction. $P < 0.05$ was taken as the significance level.

Results

General information

There were insignificant differences observed regarding age, BMI and gender between the

Table 1. Comparison of general data

Factors	AMI Group n=87	Control Group n=76	t/X^2	P
Gender			0.032	0.859
Male	47 (54.02)	40 (52.63)		
Female	40 (45.98)	36 (47.37)		
Age (years)			0.019	0.891
≥ 63	41 (47.13)	35 (46.05)		
< 63	46 (52.87)	41 (53.95)		
BMI (kg/m^2)			0.009	0.925
≥ 23	43 (49.43)	37 (48.68)		
< 23	44 (50.57)	39 (51.32)		
Smoking History			0.050	0.822
Yes	50 (57.47)	45 (59.21)		
No	37 (42.53)	31 (40.79)		
Drinking History			0.013	0.908
Yes	45 (51.72)	40 (52.63)		
No	42 (48.28)	36 (47.37)		
Educational Level			0.032	0.859
Primary School and Below	47 (54.02)	36 (47.37)		
Primary School and Above	40 (45.98)	40 (52.63)		
Combined Hypertension			0.019	0.890
Yes	41 (47.13)	35 (46.05)		
No	46 (52.87)	41 (53.95)		
Combined Diabetes			0.013	0.908
Yes	42 (48.28)	36 (47.37)		
No	45 (51.72)	40 (52.63)		

AMI: Acute Myocardial Infarction.

two groups (P > 0.05, **Table 1**), suggesting comparability between two groups.

Comparison of serum H-FABP, Copeptin and cTnI levels

The serum levels of H-FABP, Copeptin and cTnI in all patients were detected at admission, and results showed that all indicators of AMI group were evidently higher than those in control group (all P < 0.001, **Table 2**).

Comparison of serum H-FABP, Copeptin and cTnI levels among patients with different degrees of coronary artery disease

According to the degree of coronary artery disease, AMI patients were grouped into single-vessel lesion group (30 cases), double-vessel lesion group (39 cases), and three-vessel lesion group (18 cases). The serum levels of Copeptin and H-FABP in AMI patients were the highest in the three-vessel lesion group (< 0.001), and that of the double-vessel lesion group was higher markedly compared to the single-vessel lesion group (< 0.001); Serum cTnI level in AMI patients had no statistical significance among the three groups (P=0.681). Overall, it was suggested that the more severe the coronary artery disease, the higher the serum H-FABP and Copeptin levels of the patients (**Table 3**).

Diagnostic value of serum H-FABP, Copeptin and cTnI in early AMI

To determine the diagnostic value of serum H-FABP, Copeptin, and cTnI for early acute myocardial infarction, we drew ROC curves (**Figure 1**) and found that the areas under the curve of H-FABP, Copeptin and cTnI were 0.868, 0.822, and 0.803, respectively, all of which had certain diagnostic value. It should be noted that area under the H-FABP curve was greater than 0.86, showing a high clinical diagnostic value for early acute myocardial infarction. The analysis of the diagnostic value of the combined

Table 2. Comparison of serum H-FABP, Copeptin and cTnI levels between AMI and control group

Factors	AMI Group n=87	Control Group n=76	t	P
H-FABP (ng/mL)	39.58±11.69	21.84±7.37	11.40	< 0.001
Copeptin (pmol/L)	21.65±5.08	16.33±2.94	8.03	< 0.001
cTnI (ng/L)	104.05±17.43	86.2±11.74	7.554	< 0.001

H-FABP: Myocardial Fatty Acid Binding Protein; AMI: Acute Myocardial Infarction.

Table 3. Comparison of serum H-FABP, Copeptin and cTnI levels among patients with different degrees of coronary artery disease

Factors	Single-vessel Lesion Group n=30	Double-vessel Lesion Group n=39	Three-vessel Lesion Group n=18	F	P
H-FABP (ng/mL)	27.83±5.12	41.56±4.2	55.8±5.65	192.1	< 0.001
Copeptin (pmol/L)	16.29±2.57	22.51±1.85	28.74±2.41	179.4	< 0.001
cTnI (ng/L)	106.09±16.97	102.36±18.13	104.32±17.23	0.385	0.681

H-FABP: Myocardial Fatty Acid Binding Protein.

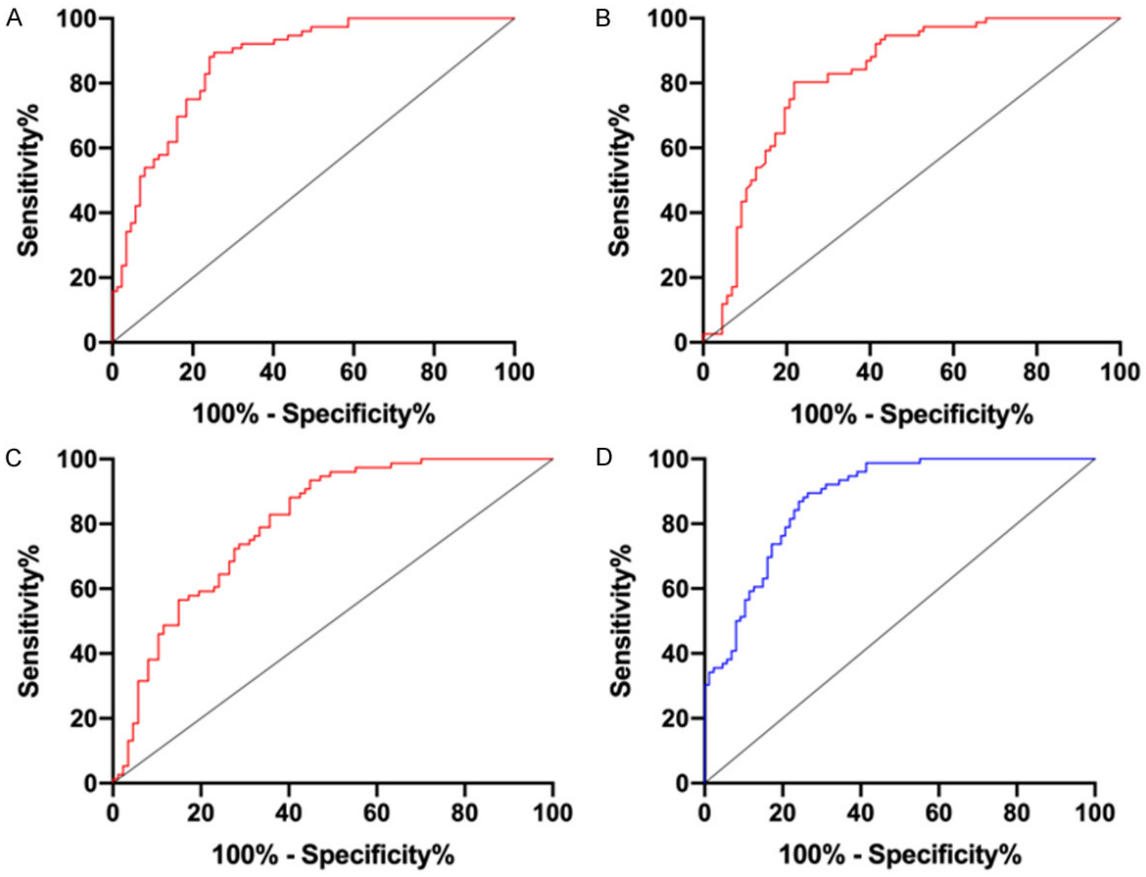

Figure 1. The diagnostic value of serum H-FABP, Copeptin and cTnI in early AMI. A. ROC curve of H-FABP for early AMI. B. ROC curve of Copeptin for early AMI. C. ROC curve of cTnI on early AMI. D. Diagnostic value of joint detection of serum H-FABP, Copeptin and cTnI in early AMI. H-FABP: Myocardial Fatty Acid Binding Protein; AMI: Acute Myocardial Infarction.

detection of serum H-FABP, Copeptin and cTnI for early acute myocardial infarction showed that the area under the curve of the joint detection was 0.880, which was larger than that of

Table 4. Diagnostic value of serum H-FABP, Copeptin and cTnI in early AMI

Predictors	AUC	95 CI%	Specificity	Sensitivity	Cut-off
H-FABP (ng/mL)	0.868	0.815-0.923	75.86%	85.53%	29.14
Copeptin (pmol/L)	0.822	0.756-0.888	64.37%	82.89%	19.53
cTnI (ng/L)	0.803	0.736-0.869	64.37%	78.95%	97.01
Joint Detection	0.880	0.829-0.930	73.56%	89.47%	0.376

H-FABP: Myocardial Fatty Acid Binding Protein; AMI: Acute Myocardial Infarction.

single detection of each index. The sensitivity and specificity of joint detection were 89.47% and 73.56% respectively, showing a markedly higher sensitivity than that of single indicators (**Table 4**).

Discussion

Coronary heart disease, especially AMI, has become one of the leading causes of disability and death among both urban and rural residents in China with a yearly rising incidence [11]. Patients suspected of AMI due to chest pain are more and more commonly seen in clinical practice recently, and early and effective diagnosis is conductive to prompting rescue and reduction in mortality rate [12]. Emergency ECG is currently often used for early diagnosis of AMI patients, but it is prone to interference and lack of diagnostic sensitivity, which can easily lead to missed diagnosis and does no good for clinical treatment [13]. Therefore, it is very necessary to find an effective method for early diagnosis of AMI.

cTnI is an important isoform of troponin that exists only in cardiomyocytes. It is released into the blood when the myocardium is damaged and this leads to an increase in serum levels, making it a more specific serum marker for myocardial damage evaluation [14]. Studies have also suggested rapid release of cTnI into the blood when myocardial damage occurs, and with its long existence, cTnI is considered to be a more sensitive marker of myocardial damage [15]. Copeptin, part of the C-terminus of preprovasopressin, is released into the blood in equal amounts by the neurohypophysis along with arginine vasopressin (AVP). Because of its good stability in blood and convenient detection, it has quickly become a surrogate marker for the detection of circulating AVP levels [16]. Early studies have shown elevated blood Copeptin levels in patients with severe infection, asthma, and stress. More and more recent studies have found that it was also closely related to cardiovascular disease, by increasing immediately in patients with AMI and gradually decreasing within five days [17]. H-FABP is a fatty acid carrier in cardiomyocytes. When myocardial cells suffer from ischemia, hypoxia and insufficient energy supply, fatty acids need to be mobilized for energy supply, and the level of HFABP in cardiomyocytes increases, which eventually leads to its increase in blood levels [18]. Due to the small molecular weight of H-FABP, the content of H-FABP in cardiomyocytes is about 10 times that of skeletal muscle, so that it can be released into the blood in a large amount in the early stage of AMI and generally begins to rise 0.5 h after its onset [19]. In this study, the levels of these three indicators were detected within 3 hours of the onset of AMI patients, and the results revealed an evident increase in the expression levels of all the three. Then, we also analyzed the levels of serum H-FABP, Copeptin and cTnI in patients with different degrees of coronary artery disease. Results showed that the higher the degree of coronary artery disease, the higher the serum H-FABP and Copeptin levels, indicating that H-FABP and Copeptin had certain predictive value for the severity of coronary artery disease. A previous study [20] also found positive correlation between the level of Copeptin and the degree of coronary artery disease. Moreover, Copeptin has a certain impact on the early diagnosis of AMI, for it is low in specificity and can be increased in acute or chronic stress states, such as respiratory tract infection, chronic obstructive pulmonary disease, heart failure, critical illness, etc. [21], which is similar to our results.

Then we also analyzed the value of these three indicators in the early diagnosis of AMI. ROC curve showed that the AUC areas for AMI prediction of the three ranked as H-FABP > Copeptin > cTnI. Among them, the areas for H-FABP and Copeptin were both over 0.8, which may be because of the relatively poor sensitivity and specificity in cTnI, for it is not only elevated in AMI, but it is also abnormal when myocardial damage is caused by various factors such

as infection, poisoning, immunity, etc. [22]. Studies have shown that high levels of H-FABP could be detected in the blood of AMI patients in their early stages of onset, and studies on Copeptin have also reported that it was of great value in the rapid exclusion of AMI [23, 24]. These results are consistent with our analysis. However, the detection of a single index still has its limitations. To further improve the accuracy of early AMI diagnosis, we analyzed the value of joint detection of serum H-FABP, Copeptin and cTnI in the early diagnosis of AMI, and it was found that the area under the ROC curve of the three-combined diagnosis was evidently larger than that of each indicator alone, which indicated that combined detection showed greater value in early AMI diagnosis than mono-detection of each three. A recent study showed that a multi-marker strategy (Copeptin and hs-cTnI measurements) was non-inferior to serial myocardial marker measurements in the diagnosis of AMI [25]. This is also our first-time analyzing value of the joint detection of H-FABP, Copeptin and cTnI in the early AMI diagnosis.

In conclusion, serum H-FABP, Copeptin and cTnI markedly elevates in the early stage of AMI. For patients with chest tightness or chest pain and suspected coronary heart disease, joint detection could be conductive to early diagnosis or exclusion of AMI and help clinicians to formulate safe diagnosis and treatment plans effectively and promptly. However, it should be pointed out that the number of selected cases of this study is quite limited, further multi-center, large-sample, large-scale research analysis and demonstration are needed in the future. In addition, the physiological and pathophysiological significance of Copeptin and H-FABP still remain unclear, therefor, basic and clinical studies are needed to clarify their roles in acute cardiovascular events, as well as their relationship with other cardiac markers.

Disclosure of conflict of interest

None.

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References

[1] Zeymer U. Diagnosis and initial management of acute myocardial infarction. MMW Fortschr Med 2019; 161: 34-36.

[2] Stengaard C, Sorensen JT, Rasmussen MB, Botker MT, Pedersen CK and Terkelsen CJ. Prehospital diagnosis of patients with acute myocardial infarction. Diagnosis (Berl) 2016; 3: 155-166.

[3] Edupuganti MM and Ganga V. Acute myocardial infarction in pregnancy: current diagnosis and management approaches. Indian Heart J 2019; 71: 367-374.

[4] DeFilippis AP, Chapman AR, Mills NL, de Lemos JA, Arbab-Zadeh A, Newby LK and Morrow DA. Assessment and treatment of patients with type 2 myocardial infarction and acute non-ischemic myocardial injury. Circulation 2019; 140: 1661-1678.

[5] Wang XY, Zhang F, Zhang C, Zheng LR and Yang J. The biomarkers for acute myocardial infarction and heart failure. Biomed Res Int 2020; 2020: 2018035.

[6] Tamis-Holland JE, Jneid H, Reynolds HR, Agewall S, Brilakis ES, Brown TM, Lerman A, Cushman M, Kumbhani DJ, Arslanian-Engoren C, Bolger AF and Beltrame JF; American Heart Association Interventional Cardiovascular Care Committee of the Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; and Council on Quality of Care and Outcomes Research. Contemporary diagnosis and management of patients with myocardial infarction in the absence of obstructive coronary artery disease: a scientific statement from the american heart association. Circulation 2019; 139: e891-e908.

[7] Park KC, Gaze DC, Collinson PO and Marber MS. Cardiac troponins: from myocardial infarction to chronic disease. Cardiovasc Res 2017; 113: 1708-1718.

[8] Ye XD, He Y, Wang S, Wong GT, Irwin MG and Xia Z. Heart-type fatty acid binding protein (H-FABP) as a biomarker for acute myocardial injury and long-term post-ischemic prognosis. Acta Pharmacol Sin 2018; 39: 1155-1163.

[9] Jeong JH, Seo YH, Ahn JY, Kim KH, Seo JY, Chun KY, Lim YS and Park PW. Performance of Copeptin for early diagnosis of acute myocardial infarction in an emergency department setting. Ann Lab Med 2020; 40: 7-14.

[10] Reinstadler SJ, Klug G, Feistritzer HJ, Metzler B and Mair J. Copeptin testing in acute myocardial infarction: ready for routine use? Dis Markers 2015; 2015: 614145.

[11] Arora G and Bittner V. Chest pain characteristics and gender in the early diagnosis of acute

myocardial infarction. Curr Cardiol Rep 2015; 17: 5.
[12] Ricci F, Neumann JT, Rubsamen N, Sorensen NA, Ojeda F, Cataldo I, Zeller T, Schafer S, Hartikainen TS, Golato M, Palermi S, Zimarino M, Blankenberg S, Westermann D and De Caterina R. High-sensitivity troponin I with or without ultra-sensitive Copeptin for the instant rule-out of acute myocardial infarction. Front Cardiovasc Med 2022; 9: 895421.
[13] Vafaie M. State-of-the-art diagnosis of myocardial infarction. Diagnosis (Berl) 2016; 3: 137-142.
[14] Fan J, Ma J, Xia N, Sun L, Li B and Liu H. Clinical value of combined detection of CK-MB, MYO, cTnI and Plasma NT-proBNP in diagnosis of acute myocardial infarction. Clin Lab 2017; 63: 427-433.
[15] Liu WC, Lin CS, Tsai CS, Tsao TP, Cheng CC, Liou JT, Lin WS, Cheng SM, Lou YS, Lee CC and Lin C. A deep learning algorithm for detecting acute myocardial infarction. EuroIntervention 2021; 17: 765-773.
[16] Budnik M, Bialek S, Peller M, Kiszkurno A, Kochanowski J, Kucharz J, Sitkiewicz D and Opolski G. Serum Copeptin and Copeptin/NT-proBNP ratio - new tools to differentiate takotsubo syndrome from acute myocardial infarction. Folia Med Cracov 2020; 60: 5-14.
[17] Keller T, Tzikas S, Zeller T, Czyz E, Lillpopp L, Ojeda FM, Roth A, Bickel C, Baldus S, Sinning CR, Wild PS, Lubos E, Peetz D, Kunde J, Hartmann O, Bergmann A, Post F, Lackner KJ, Genth-Zotz S, Nicaud V, Tiret L, Munzel TF and Blankenberg S. Copeptin improves early diagnosis of acute myocardial infarction. J Am Coll Cardiol 2010; 55: 2096-2106.
[18] Sotoudeh Anvari M, Karimi M, Shafiee A, Boroumand M, Bozorgi A, Sedaghat R and Jalali A. Complementary diagnostic value of heart type fatty acid-binding protein in early detection of acute myocardial infarction. Crit Pathw Cardiol 2018; 17: 43-46.
[19] Jacobs LH, van Borren M, Gemen E, van Eck M, van Son B, Glatz JF, Daniels M and Kusters R. Rapidly rule out acute myocardial infarction by combining Copeptin and heart-type fatty acid-binding protein with cardiac troponin. Ann Clin Biochem 2015; 52: 550-561.
[20] Choi HJ, Kim MC, Sim DS, Hong YJ, Kim JH, Jeong MH, Kim SH, Shin MG and Ahn Y. Serum Copeptin levels predict clinical outcomes after successful percutaneous coronary intervention in patients with acute myocardial infarction. Ann Lab Med 2018; 38: 538-544.
[21] Yang Y, Gao S, Fang Q and Yang J. Diagnostic value of Copeptin combined with hypersensitive cardiac troponin T detection in early acute myocardial infarction: a protocol of randomized double-blind diagnostic trial. Medicine (Baltimore) 2021; 100: e23949.
[22] Su T, Shao X, Zhang X, Yang C and Shao X. Value of circulating miRNA-1 detected within 3 h after the onset of acute chest pain in the diagnosis and prognosis of acute myocardial infarction. Int J Cardiol 2020; 307: 146-151.
[23] Lefevre G, Fayet JM, Graine H, Berny C, Maupas-Schwalm F, Capolaghi B and Morin C. Multicenter evaluation of h-FABP semi-quantitative assay (Cardio Detect) in central laboratory: the point in acute myocardial infarction diagnosis. Ann Biol Clin (Paris) 2007; 65: 377-384.
[24] Ray P, Charpentier S, Chenevier-Gobeaux C, Reichlin T, Twerenbold R, Claessens YE, Jourdain P, Riou B and Mueller C. Combined Copeptin and troponin to rule out myocardial infarction in patients with chest pain and a history of coronary artery disease. Am J Emerg Med 2012; 30: 440-448.
[25] Kim KS, Suh GJ, Song SH, Jung YS, Kim T, Shin SM, Kang MW and Lee MS. Copeptin with high-sensitivity troponin at presentation is not inferior to serial troponin measurements for ruling out acute myocardial infarction. Clin Exp Emerg Med 2020; 7: 35-42.