Original Article

Analysis of correlation between heart failure in the early stage of acute myocardial infarction and serum pregnancy associated plasma protein-A, prealbumin, C-reactive protein, and brain natriuretic peptide levels

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Background: The study sought to analyze the predictive value of the early measurement of pregnancy associated plasma protein-A (PAPP-A), prealbumin (PAB), C-reactive protein (CRP), brain natriuretic peptide (BNP), and other indicators of heart failure (HF) after acute myocardial infarction (AMI).

Methods: A total of 200 AMI patients admitted to Wuyi People's Hospital from November 1, 2019 to October 31, 2020 were continuously enrolled as the research objects and divided into a HF group (Killip class II or above, n=94) and HF-free group (Killip class I or below, n=106) according to the Killip Classification for Heart Function.

Results: The age, creatine kinase-myocardial band (CK-MB), PAPP-A, CRP, suppression of tumorigenicity 2 (ST2), BNP, aldosterone (ALD), and left ventricular end-diastolic diameter (LVEDD) of the HF group were all significantly higher than those of the HF-free group, while the PAB and left ventricular ejection fraction (LVEF) were significantly lower (P<0.05). The PAPP-A, CRP, and BNP of HF patients increased as the Killip class increased, while the PAB decreased progressively (P<0.05). After including the statistically significant single factors in a multivariate logistic regression analysis, it was found that PAPP-A, PAB, CRP, and BNP were the independent influencing factors causing HF in the early stage of AMI; and the diagnostic efficacy of HF in the early stage of AMI (from high to low) was combined test, PAPP-A, PAB, BNP and CRP.

Conclusions: Serum PAPP-A, PAB, CRP and BNP levels are the independent influencing factors of HF after AMI, but comprehensive tests of clinical indicators, including PAPP-A, PAB, CRP, and BNP, are more accurate at predicting and evaluating HF and can be used to guide clinical decisions.

Keywords: Acute myocardial infarction (AMI); correlation analysis; early heart failure

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Introduction

Acute myocardial infarction (AMI) mostly occurs on the basis of coronary atherosclerotic stenosis. After the rupture of coronary atherosclerotic plaques caused by some incentives, platelets gather on the surface of the ruptured plaques to form blood clots (thrombus), which suddenly block the coronary artery lumen, leading to myocardial ischemia and necrosis, accompanied by left heart failure (1-4). In addition, AMI combined with acute heart failure (AHF) is often associated with the myocardial infarction range, and the complications of various diseases such as hypertension, diabetes and hyperlipidemia in elderly patients are also important factors triggering heart failure (HF). If the occurrence of HF could be predicted by the early detection of a certain indicator and timely treatments could be administered in clinic, patient outcomes could be greatly improved, which is also the key and major difficulty in current clinical research. Brain natriuretic peptide (BNP), a cardiovascular peptide hormone, is a sensitive and specific detection indicator for cardiac dysfunction, and C-reactive protein (CRP), a sensitive acute phase protein, significantly increases in acute inflammation. Related studies at home and abroad have shown that BNP and CRP levels have advantages in the diagnosis of early HF after AMI, and have certain clinical value for the prognosis of patients (5-8). Through the analysis of relevant literature, it is found that serum pregnancy-associated plasma protein A (PAPP-A) was first found in pregnancy serum, and has subsequently been applied in obstetrics and gynecology research. In recent years, some studies have shown that PAPP-A directly promotes the occurrence and progression of atherosclerotic plaque (9-12). Prealbumin (PAB), a kind of negative acute phase response protein that is often detected in clinical settings, is involved in the pathological process of many diseases through an inflammatory response mechanism. PAB also suggests the reduction degree of cardiac contractile function in HF patients. However, there are few studies on the relationship between PAPP-A or PAB and HF after AMI in China. In addition, the relationship between PAPP-A and PAB, the products and participants of inflammatory response after AMI, has not been reported. Additionally, tests that combine PAPP-A and PAB with C-reactive protein (CRP) and brain natriuretic peptide (BNP) have greater sensitivity and specificity and prevent the development of adverse outcomes in patients with HF. Thus, this study sought to examine the correlations between PAPP-A, PAB, and other indicators at the early onset of AMI and HF after AMI to provide a basis for clinical decisions. We present the following article in accordance with the STARD reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-21-2993/rc).

Methods

General information

A total of 200 AMI patients (aged 55–78 years old) who were admitted to Wuyi People's Hospital from November 1, 2019 to October 31, 2020 were continuously enrolled as the research objects in this study, and divided into either the HF group (Killip class II or above II, n=94) or the HF-free group (Killip class I or below, n=106) according to the Killip Classification for Heart Function. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013) (13). The study was approved by ethics committee of Wuyi People's Hospital (approval No. 20190951) and individual consent for this retrospective analysis was waived.

Inclusion criteria

Patients were included in the study if they met the following inclusion criteria: (I) met the diagnosis criteria for AMI; that is, acute chest pain (onset <12 h) with or without increased myocardial enzymes, and with 1 of the following imaging features: obvious ST segment elevation or Q waves in an electrocardiogram (ECG), a regional motion abnormality suggested by cardiac ultrasonography or coronary artery stenosis, or infarction clearly presented in emergency coronary angiography; (II) had an onset time <12 h; and (III) were aged 55–78 years old. AMI accompanied by heart failure is more common in patients over 55 years old, but patients with too high age had impaired physical function, which may affect the objectivity and scientificity of the study. So the maximum age of the enrolled patients was 78 years old.

Exclusion criteria

Patients were excluded from the study if they met any of the following exclusion criteria: (I) had a history of myocardial disease; and/or (II) had other acute damage in important organs, such as the lungs, kidneys, or liver.

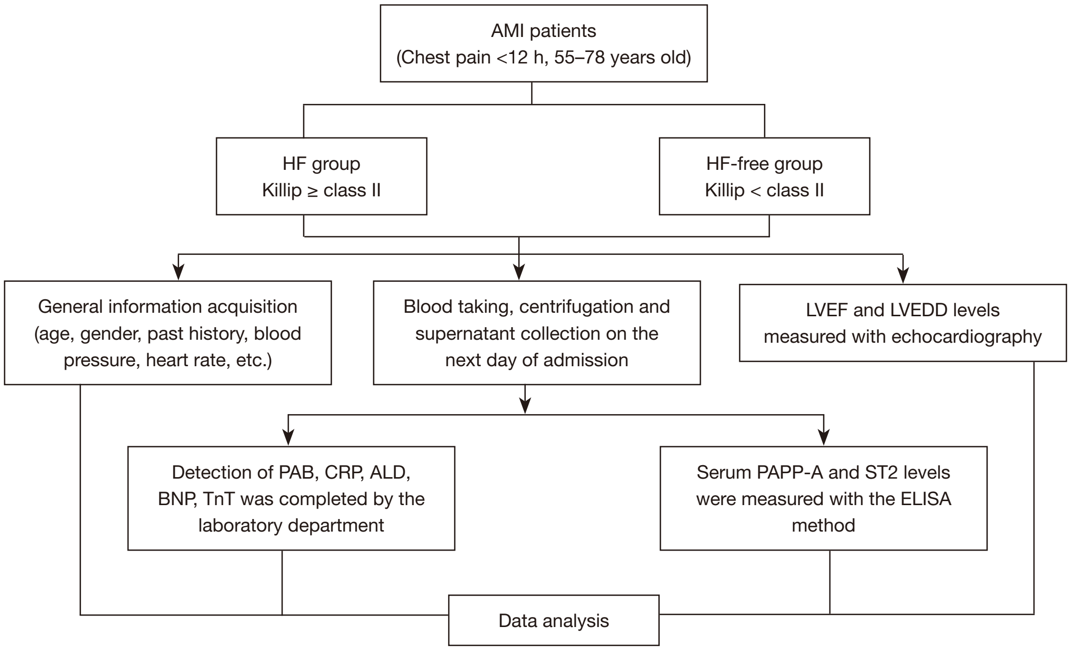

Figure 1 Study flow chart. AMI, acute myocardial infarction; HF, heart failure; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; PAB, prealbumin; CRP, C-reactive protein; ALD, aldosterone; BNP, brain natriuretic peptide; TnT, troponin T; PAPP-A, pregnancy associated plasma protein-A; ST2, tumorigenicity 2.

Study methods and observation indexes

After admission, the patients' general clinical information, including age, gender and past medical history, were collected, and the following biochemical index detection procedure was used: 10–15 mL of fasting peripheral vein blood was drawn from each patient in the morning, and solidified at room temperature for 10–20 min, after which it was centrifuged for 20 min under 2,000–2,000 r/min; finally, the supernatant was the collected and kept at low temperature until the analysis was conducted (14,15).

The levels of blood glucose, blood lipid, CRP, PAB, creatine kinase-myocardial band (CK-MB), troponin T (TnT), and aldosterone (ALD) were measured with a fully automated biochemical analyzer. BNP level was measured with a fully automated electrochemistry analyzer. PAPP-A and suppression of tumorigenicity 2 (ST2) levels were measured with an enzyme linked immunosorbent assay (ELISA). The left ventricular ejection fraction (LVEF) and left ventricular end-diastolic diameter (LVEDD) of patients were detected by echocardiography. The above observation indexes were detected in the laboratory department of our hospital. *Figure 1* shows a detailed flow chart of the study.

Statistical analysis

The data analysis was conducted with SPSS23.0 software. The enumeration data are expressed as [n (%)] and were examined with a χ^2 test. Spearman or Pearson tests were used to conduct the correlation analyses. The measurement data are expressed as ($\bar{x}$±s), and *t*-tests were used for between-group comparisons. A logistic stepwise regression analysis was performed to examine the relevant parameters and independent risk factors. Differences with a P value <0.05 were considered statistically significant.

Results

Comparison of clinical information between the two groups

The age, CK-MB, PAPP-A, CRP, ST2, BNP, ALD, and LVEDD of the HF group were significantly higher than those of the HF-free group, while the PAB and LVEF were significantly lower (P<0.05; see *Table 1*).

Table 1 Clinical information

Indicators	HF group (n=94)	HF-free group (n=106)	t/χ^2	P
Age (years)	58.16±5.31	53.92±5.06	5.7787	<0.001
Gender (male/female)	50/44	55/51	0.0340	0.854
Hypertension, n (%)	35 (37.23)	32 (30.19)	1.1101	0.292
Diabetes, n (%)	20 (21.28)	15 (14.15)	1.7521	0.186
Hyperlipidemia, n (%)	20 (21.28)	20 (18.87)	0.1807	0.671
TnT (ng/L)	6.75±1.19	6.64±1.13	0.6702	0.5035
CK-MB (U/L)	77.83±15.76	68.04±13.15	4.7871	<0.001
PAPP-A (pg/mL)	34.08±6.79	25.47±6.25	9.3363	<0.001
PAB (mg/L)	145.09±35.13	183.86±40.85	7.1506	<0.001
Triglyceride (mmol/L)	3.02±0.81	3.11±0.85	0.7640	0.4458
Total cholesterol lipoprotein (mmol/L)	7.16±1.85	7.08±1.81	0.3087	0.7578
Low density lipoprotein (mmol/L)	3.17±0.93	3.15±0.88	0.1562	0.8760
CRP (mg/L)	15.48±3.02	10.67±2.61	12.0819	<0.001
ST2 (μg/L)	36.59±3.54	30.71±4.43	10.2820	<0.001
BNP (pg/mL)	746.23±121.34	589.26±98.35	6.8161	<0.001
ALD (ng/L)	235.37±16.05	216.33±12.35	9.4585	<0.001
LVEF (%)	42.93±9.81	50.06±10.52	4.9668	<0.001
LVEDD (mm)	60.84±6.15	51.75±5.96	10.6623	<0.001

P values indicate random variables obeying normal distribution in the probability model; P<0.05 indicates that the differences are statistically significant. TnT, troponin T; CK-MB, creatine kinase-myocardial band; PAPP-A, pregnancy associated plasma protein-A; PAB, prealbumin; CRP, C-reactive protein; ST2, suppression of tumorigenicity 2; BNP, brain natriuretic peptide; ALD, aldosterone; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter.

Changes in indicators for different Killip classes of patients with AMI complicated by HF

As the Killip class increased, the PAPP-A, CRP, and BNP of HF patients increased, while PAB decreased progressively (P<0.05; see *Table 2*).

Multivariate regression analysis of HF in the early stage of AMI

A multivariate logistic regression analysis was undertaken of the statistically significant single factors in which the dependent variable was whether or not there was a complication of HF (HF =1). The results showed that PAPP-A, PAB, CRP, and BNP were the independent influencing factors causing HF in the early stage of AMI (see *Table 3*).

Efficacy of each index for diagnosing HF in the early stage of AMI

It was concluded from the receiver operating characteristic (ROC) that the diagnostic efficacy of HF in the early stage of AMI (from high to low) was combined test, PAPP-A, PAB, BNP and CRP (see *Figure 2* and *Table 4*).

Discussion

As a result of advances in medical technology levels in recent years, the survival rate of AMI patients has gradually increased; however, HF remains the main cause of poor patient prognosis. Presently, the early identification of high-risk individuals with HF and the optimization of individualized treatment regimens are difficult, but popular, areas of clinical research (16). Previously, multiple studies

Table 2 Changes in indicators under different Killip classes ($\bar{x}$±s)

Indicators	Class II (n=42)	Class III (n=30)	Class IV (n=22)	F	P
PAPP-A (pg/mL)	27.45±5.21	33.19±6.08	39.68±6.11	9.76	<0.001
PAB (mg/L)	179.85±32.14	156.07±24.18	123.26±26.87	10.58	<0.001
CRP (mg/L)	10.76±2.33	13.4±3.07	16.78±3.15	8.52	<0.001
BNP (pg/mL)	386.63±46.32	608.23±45.16	854.71±42.01	11.54	<0.001

F-test is a test in which the statistical values follow the F-distribution under the null hypothesis (null hypothesis, H0), which is often used to analyze the statistical models with more than one parameter. F values are the statistical values of the F test. P values indicated random variables obeying normal distribution in the probability model; P<0.05 indicates that the differences are statistically significant. PAPP-A, pregnancy associated plasma protein-A; PAB, prealbumin; CRP, C-reactive protein; BNP, brain natriuretic peptide.

Table 3 Logistic regression analysis

Indicators	B	S.E	Wals	df	Sig.	EXP (B)	95% CI of EXP (B)
Age	0.033	0.040	0.673	1	0.412	1.034	0.955–1.070
PAPP-A	3.731	0.846	19.463	1	0.000	41.741	7.954–219.041
PAB	–0.220	0.039	32.363	1	0.000	0.803	0.744–0.866
CRP	1.249	0.186	45.049	1	0.000	3.485	2.420–5.019
CK-MB	0.015	0.027	0.293	1	0.588	1.1015	0.962–1.070
ST2	–0.051	0.050	1.053	1	0.305	0.950	0.862–1.047
BNP	0.043	0.007	34.932	1	0.000	1.044	1.029–1.059
ALD	0.013	0.016	0.649	1	0.412	1.013	0.981–1.046
LVEF	0.004	0.025	0.022	1	0.882	1.004	0.956–1.054
LVEDD	0.019	0.031	0.368	1	0.544	1.019	0.959–1.082

B, regression coefficient; S.E, standard error; Wald values, Wald statistic probability values; df, degrees of freedom; Sig., P values; EXP (B), OR values; PAPP-A, pregnancy associated plasma protein-A; PAB, prealbumin; CRP, C-reactive protein; CK-MB, creatine kinase-myocardial band; ST2, suppression of tumorigenicity 2; BNP, brain natriuretic peptide; ALD, aldosterone; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter.

(17,18) have shown that the detection levels of plasma BNP and CRP in patients effectively predict the prognosis of AMI patients, but their sensitivity and specificity for predicting HF are low. Thus, a test that combines other indicators is required to improve predictions of HF after AMI. Previous research on the inflammatory factor of PAPP-A in the cardiovascular field has mainly focused on aspects such as atherosclerosis and myocardial infarction; however, research on the correlation between of PAPP-A and HF remains inconclusive. Gaber (19) and others previously reported that PAPP-A was most likely involved in the process of ventricular remodeling after AMI and closely related to HF. Thus, PAPP-A likely has high research value in predicting HF after AMI. PAB is a non-specific host defense substance that is gradually consumed after AMI in the process of clearing toxic products. A post-AMI inflammatory reaction and autoimmune reaction also further contribute to a decline in PAB levels (20). Consequently, the levels of PAB in AMI patients with HF are not only lower than normal levels, but may even be lower than those in AMI patients without HF. At present, very few studies have been conducted on the relationship among PAPP-A, PAB, and post-AMI HF in China. Thus, this study sought to actively investigate correlations between the levels of PAPP-A, PAB, CRP, and BNP and post-AMI HF, to provide a theoretical basis for the prevention and treatment of post-AMI HF.

The general clinical information of patients in both groups were first analyzed in this study, and it was concluded that age, CK-MB, PAPP-A, CRP, ST2, BNP, ALD, and LVEDD were significantly higher in the HF group than in

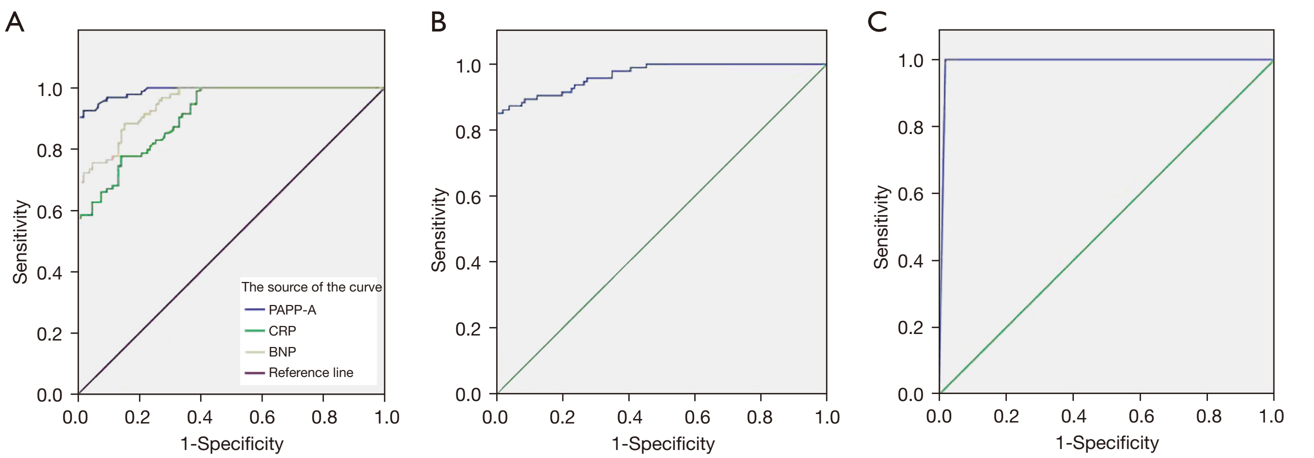

Figure 2 Analysis of the diagnosis value of each indicator of HF in the early stage of AMI with ROC curves. (A) The ROC curves of PAPP-A, BNP, and CRP for diagnosing HF in the early stage of AMI; (B) the ROC curve of PAB for diagnosing HF in the early stage of AMI; (C) the ROC curve of the combined test for diagnosing HF in the early stage of AMI. HF, heart failure; AMI, acute myocardial infarction; ROC, receiver operating characteristic; PAPP-A, pregnancy associated plasma protein-A; BNP, brain natriuretic peptide; CRP, C-reactive protein.

Table 4 Areas under the ROC curves

Test variables	Area	Standard error[a]	Progressive significance[b]	95% CI of progression
Combined test	0.991	0.008	0.000	0.000–1.000
PAPP-A	0.990	0.005	0.000	0.981–0.999
PAB	0.967	0.011	0.000	0.946–0.988
BNP	0.950	0.013	0.000	0.925–0.976
CRP	0.909	0.019	0.000	0.872–0.946

[a], under nonparametric hypothesis; [b], Null hypothesis, solid area =0.5. ROC, receiver operating characteristic; PAPP-A, pregnancy associated plasma protein-A; PAB, prealbumin; BNP, brain natriuretic peptide; CRP, C-reactive protein.

the HF-free group, while PAB and LVEF were significantly lower (P<0.05). Thus, it was suggested that these indicators might be associated with the occurrence of HF after AMI. A review of the previous relevant literature revealed that Sinha *et al.* (21) similarly reported that the CRP and BNP indexes were significantly higher and LVEF indexes were significantly lower in post-AMI HF patients than in patients without HF, which is consistent with the findings of the present study. An in-depth analysis of the relationship among each of the above-mentioned indexes and the functional class of the HF patients showed that the levels of PAPP-A, CRP, and BNP all increased as Killip class increased, while the level of PAB declined progressively (P<0.05). These results indicated that the levels of PAPP-A, PAB, CRP, and BNP all reflect cardiac function changes in AMI patients. The statistically significant variables identified in the univariate analysis were then incorporated into the logistic regression analysis, and the results showed that PAPP-A, PAB, CRPl, and BNP were all independent factors that contributed to the development of HF in the early stage of AMI. Finally, the diagnostic efficacy of PAPP-A, PAB, CRP, and BNP for HF in the early stage of AMI was investigated. The diagnostic efficacy of HF in the early stage of AMI (from high to low) was combined test, PAPP-A, PAB, BNP and CRP, suggesting that both PAPP-A and PAB levels were associated with the development of HF after AMI with a high detection efficacy. But the traditional indexes, such as the BNP and CRP indexes, could not be completely put aside as both BNP and CRP had value in predicting the disease. PAPP-A and PAB combined with BNP and CRP testing provided a more comprehensive reflection of disease changes, had higher predictive value in predicting early cardiac function changes than BNP and CRP, and thus should be used to make timely clinical adjustment in treatment strategies.

After analyzing the mechanisms involved, we found that sustained myocardial infarction and other factors reduce cardiac contractility, leading to a large secretion of neurohormones and the overexpression of proinflammatory factors. Oxidative stress is an important cause of myocardial cell apoptosis and reduces function. Further, the cell damage caused by oxidative stress can upregulate the amount of PAPP-A expression and then trigger the cascade reaction of inflammatory factors. A correlation between PAPP-A and the degree of HF after AMI was confirmed. PAB is involved in the inflammatory response after myocardial infarction and can clear toxic metabolic substances during the inflammatory infection phase; thus, its level decreases with the occurrence of HF (22-25). Consequently, both PAPP-A and PAB are important references in predicting HF in the early stage of AMI. When the heart is ischemic or hypoxic, the ventricular myocardium is stretched, which stimulates the heart to synthesize and secrete BNP that can inhibit the activation of the renin-angiotensin-aldosterone system and sympathetic nervous system, prevent cardiac remodeling, and alleviate HF. Thus, there is great value in determining the BNP levels of patients with HF after AMI. CPR provides no specificity in disease diagnosis; however, its elevated concentration is a sensitive index for inflammation and tissue damage. Thus, the simultaneous measurement of PAPP-A and PAB levels together with BNP and CRP indicators significantly improve the prediction of the likelihood of HF in AMI. In addition, the key to reducing the mortality of patients is timely diagnosis and treatment of AMI, targeted improvement of cardiac systolic and diastolic function in the treatment of acute left heart failure, strengthening monitoring, and proper treatment of various complications. Early coronary angiography and coronary revascularization should be performed in patients without contraindications and with unsatisfactory results of conventional drug therapy to save the dying myocardium and prevent the extension of infarction or the occurrence of new myocardial infarction, which is expected to significantly improve the early prognosis of patients.

This study had a number of limitations. First, in this study, PAPP-A may have independent value in predicting HF after AIM, especially in the treatment of inflammatory response within atherosclerotic plaques. However, as a biological indicator, PAPP-A alone has limitations in the prediction of HF after AMI. It is more beneficial to grasp the occurrence and development of HF after AMI when combining PAPP-A with indicators such as PAB, CRP, BNP, ST2, and ALD in clinical treatment. Second, the collection of data from a single-center data might have led to selection bias; however, the value and significance of PAPP-A, PAB, CRP, and BNP in predicting HF in early AMI were confirmed to some extent by the multivariate comparative analysis. We intend to conduct a multi-center large sample-size study in the future to further explore changes in PAPP-A and PAB before and after treatment and their value in determining the prognosis of AMI patients.

In conclusion, serum PAPP-A, PAB, CRP, and BNP levels are independent influencing factors causing HF after AMI. The comprehensive testing of PAPP-A, PAB, CRP, BNP, and other clinical indicators is beneficial in the prediction and evaluation of HF in the early stage of AMI and can be used to guide clinical decisions.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-21-2993/rc

Data Sharing Statement: Available at https://apm.amegroups.com/article/view/10.21037/apm-21-2993/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-21-2993/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics committee of Wuyi People's Hospital (approval No. 20190951) and individual consent for this retrospective analysis was waived.

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