

Original Article

Predictive value of NT-proBNP, procalcitonin and CVP in patients with new-onset postoperative atrial fibrillation after cardiac surgery

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Abstract: Objective: To investigate the predictive value of N-terminal pro brain natriuretic peptide (NT-proBNP), procalcitonin and central venous pressure (CVP) for new atrial fibrillation after cardiac surgery. Methods: Patients underwent cardiac surgery in Huai'an First People's Hospital from June 2019 to December 2020 were enrolled in this study. Patients without POAF after surgery were included in the control group, and patients with POAF after surgery were included in the POAF group. Clinical data of patients were collected and retrospectively analyzed. Results: The incidence of in-hospital complications, length of stay and cost of hospitalization in the POAF group were significantly higher than those in the control group; Moreover, there were significant differences in central venous pressure, peak cTnl, NT-proBNP, procalcitonin, and white blood cell counts between the two groups. NT-proBNP, procalcitonin and elevated central venous pressure are independent risk factors for POAF in patients after cardiac surgery. Conclusion: NT-proBNP, procalcitonin and CVP were closely related with atrial fibrillation after cardiac surgery. The combination of NT-proBNP, procalcitonin and CVP had a better discriminative ability for new atrial fibrillation after cardiac surgery compared to either of them alone.

Keywords: Cardiac surgery, atrial fibrillation, serum markers

Introduction

Postoperative atrial fibrillation (POAF) is considered as the most commonly faced supra-ventricular arrhythmia after cardiovascular surgery. The incidence of POAF after cardiac surgery is about 20%-50%, especially for valve and bypass surgery [1, 2]. Studies have shown that POAF is related to many factors, including obesity [3], gender, chronic obstructive disease, valvular heart disease [4, 5], epicardial adipose tissue [6], and obstructive sleep apnea [7]. But the exact mechanism is still unclear. The onset and development of POAF was associated with inflammation, cardiac ischemia and sympathetic activation. POAF not only increases the length of hospitalization and hospitalization costs, but also increases the incidence of perioperative complications and mortality, leading to a poor prognosis.

Therefore, preventing the occurrence of POAF after cardiac surgery and finding the specific biomarkers for the prediction are particularly important.

It has been reported that procalcitonin could predict the incidence of POAF after cardiac surgery, including coronary artery bypass grafting [8]. There are increased evidences which revealed that elevated level of N-terminal pro brain natriuretic peptide (NT-proBNP) was correlated with postoperative major adverse cardiovascular events in general and POAF in particular [9]. Central venous pressure (CVP), one of the most common hemodynamic indexes, is increased in response to various stimuli including elevated wall stress and fulfilling pressure, and cardiac ischemia [10]. Nevertheless, there is still a lack of ideal biomarkers for early prediction of POAF. The aim of this study was to

Combined serum markers in POAF patients

explore the independent risk factors for new atrial fibrillation after cardiac surgery, and at the same time to construct a joint predictive model with multiple risk factors and to evaluate its predictive value, so as to guide prevention and early treatment of the new atrial fibrillation after cardiac surgery.

Materials and methods

Research objects

In this retrospective study, patients who underwent cardiac surgery in Huai'an First People's Hospital from June 2019 to December 2020 were consecutively included. POAF is defined as any documented atrial fibrillation episode lasting >30 seconds captured on a standard 12-lead electrocardiogram during the period from immediately after cardiac surgery to discharge. This study was approved by the ethics committee of Huai'an First People's Hospital (Approval number: 2019214) and complied with "Declaration of Helsinki" revised in 2013. The research subjects were exempted from signing informed consent for the retrospective nature.

The inclusion criteria were as follows: patients who underwent the elective first cardiac surgery; patients with confirmed sinus rhythm before surgery; patients with an age over 18 years old; and patients with completed data. The exclusion criteria were as follows: patients were with previous paroxysmal atrial fibrillation; patients were diagnosed as primary cardiomyopathy or congenital heart disease; or patients with implanted cardiac devices and electrophysiologic ablation history.

Research groups

According to the occurrence of POAF, patients without POAF were included in the control group, and patients with POAF were included in the POAF group. The POAF group was treated with amiodarone (Sanofi Company, France) according to the conventional regimen to treat new postoperative POAF. According to the recommendations, a loading dose of amiodarone 150 mg was given intravenously, then the maintenance amiodarone was intravenously given with 0.5-2 mg per minute. This intravenous medication was gradually switched to oral

dosing. The oral amiodarone (200 mg three times daily starting 5 days and 200 mg once daily continuing for one month) was performed in patients after surgery.

Collection of clinical data

Clinical data of selected patients were collected from the electronic medical record system, including: (1) Basic information: gender, age, New York heart function classification at admission, length of stay (days) and cost; (2) Past medical history: Diabetes, hypertension, coronary heart disease, mean arterial pressure and heart rate; (3) Clinical prognosis: perioperative complications include stroke, hemorrhage, infection, renal function or respiratory failure, cardiac arrest, and cerebral complications; (4) Laboratory Data and auxiliary examination: preoperative and postoperative white blood cell count, procalcitonin, NT-proBNP and cardiac troponin I (cTnI) which were detected by C6000 type automatic biochemistry analyser (Roche, USA). Central venous pressure was detected through the insertion of a catheter into a jugular vein.

The primary outcomes included new onset of postoperative atrial fibrillation, white blood cell count, procalcitonin, NT-proBNP, cTnI and central venous pressure. The secondary outcomes consisted of in-hospital complication rate, mortality, hospital stay and hospital costs.

Statistical analysis

SPSS 20.0 software and MedCalc 19.3 software were used for data analysis. Normally distributed measurement data were expressed as Mean \pm standard deviation (SD), and the independent sample t test was used for comparison between groups. Enumeration data were expressed as a percentage (%), and the chi-square test was used for comparison between groups. The control group and the POAF group were matched at 1:1 by the nearest neighbor matching method. The variables with $P < 0.05$ in the univariate analysis were incorporated into the multivariate logistic regression model to analyze the independent risk factors for POAF in patients after cardiac surgery, and the logistic model equation was used to transform to construct the combined predictive factor, according to the work of the subjects. The receive-

Combined serum markers in POAF patients

Table 1. Comparison of hospitalization outcomes between POAF group and normal control group

Group	In-hospital complication rate N (%)	Mortality N (%)	Hospital stay (days)	Hospital costs [Ten thousand, M (Q1, Q3)]
POAF group (n=71)	11 (15.5)	2 (2.8)	15.1±3.3	11.2 (8.9, 13.1)
Control group (n=66)	4 (6.1)	1 (1.5)	11.6±2.1	7.4 (6.5, 8.5)
χ^2 /t/Z value	4.468	0.271	7.343	4.574
P value	0.035	0.603	<0.001	<0.001

Table 2. Comparison of baseline clinical data between two groups of patients after propensity matching

Project	Control group (n=49)	POAF group (n=49)	χ^2 /t Value	P Value
Age (years)	61.3±3.1	62.5±2.6	1.730	0.087
Male [N (%)]	28 (57.1)	26 (53.1)	0.165	0.685
Heart rate (bpm/min)	78.1±11.3	76.9±14.2	0.463	0.645
Mean arterial pressure (mmHg)	81.9±15.7	83.4±16.1	0.467	0.642
Diabetes [N (%)]	15 (30.6)	16 (32.6)	0.047	0.828
Hypertension [N (%)]	14 (28.6)	15 (30.6)	0.049	0.825
Coronary heart disease [N (%)]	13 (26.5)	13 (26.5)	0.000	>1.000

Table 3. Comparison of central venous pressure combined serum markers between two groups

Parameters	Control group (n=49)	POAF group (n=49)	t/Z Value	P Value
Central venous pressure (mmHg)	9.1±2.7	14.7±3.5	5.237	0.005
cTnl peak [μ g/L, M (Q1, Q3)]	1.2 (0.7, 1.3)	3.8 (3.1, 4.2)	8.047	0.003
NTproBNP [ng/L, M (Q1, Q3)]	1024 (935, 1176)	3679 (3082, 4249)	6.556	0.006
Procalcitonin [ng/ml, M (Q1, Q3)]	0.6 (0.4, 0.9)	1.7 (1.5, 2.1)	3.932	0.008
White blood cell count ($\times 10^9$ /L)	11.2±2.5	16.7±3.9	8.553	0.002

er operating characteristic (ROC) curve was used to determine the predictive performance of the screened factors. The difference was statistically significant with $P < 0.05$.

Results

Comparison of hospitalization outcomes

A total of 137 patients who underwent cardiac surgery were included in this study, including 66 in the normal control group and 71 in the POAF group. The incidence of in-hospital complications, length of stay, and cost of hospitalization in the POAF group were significantly higher than those in the normal control group (all $P < 0.05$, **Table 1**).

Comparison of general information

Taking into account the large difference in sample size between the two groups and the

large number of observation indicators, in order to ensure the comparability between the two groups, the propensity score matching was carried out on the two sets of samples. After matching the patients in the normal control group and the POAF group with 1:1, the patients who finally matched successfully constitute a new data set for further statistical analysis. Comparison of baseline clinical data between two groups of patients after matching age, gender, preoperative heart rate, preoperative mean arterial pressure, percentage of patients with a history of diabetes, percentage of patients with a history of hypertension, and a history of coronary heart disease, showed that there were no statistically significant differences in baseline data (all $P > 0.05$, **Table 2**). The differences in central venous pressure, peak cTnl, NT-proBNP, procalcitonin, and white blood cell counts between the two groups were statistically significant ($P < 0.01$) (**Table 3** and **Figure 1**).

Combined serum markers in POAF patients

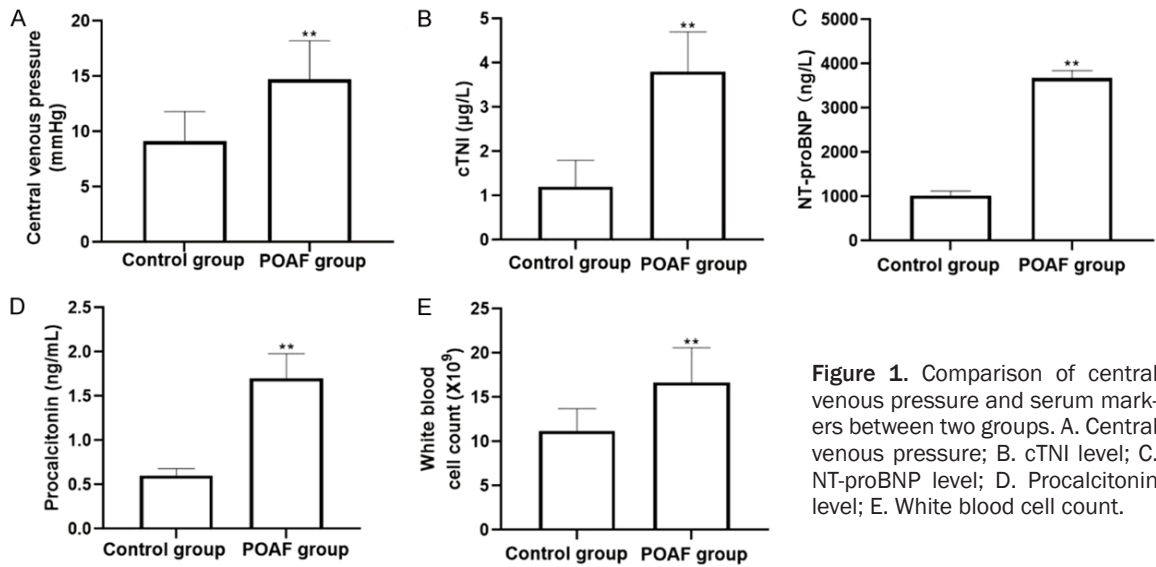


Figure 1. Comparison of central venous pressure and serum markers between two groups. A. Central venous pressure; B. cTNI level; C. NT-proBNP level; D. Procalcitonin level; E. White blood cell count.

Table 4. Univariate analysis of the risk factors for POAF after cardiac surgery

Factors	β value	OR value	95% CI	P value
Central venous pressure	0.036	1.078	0.842-1.312	0.009
cTnl peak	-0.015	0.862	0.764-1.239	0.105
NT-proBNP	0.031	1.062	0.911-1.352	0.032
Procalcitonin	0.312	1.289	1.042-1.624	<0.001
White blood cell count	-0.009	0.939	0.887-1.025	0.305

Table 5. Multivariate logistic regression analysis results of POAF after cardiac surgery

Factors	β value	OR value	95% CI	P value
Central venous pressure	0.028	1.092	0.911-1.239	0.011
cTnl peak	-0.010	0.901	0.811-1.097	0.093
NT-proBNP	0.026	1.011	0.935-1.212	0.021
Procalcitonin	0.249	1.179	1.036-1.412	<0.001
White blood cell count	-0.011	0.946	0.936-1.011	0.288

Univariate and multivariate analysis of the factors for POAF after cardiac surgery

The factors with statistical significance in the univariate analysis were brought into the multivariate logistic regression model, and the analysis results showed that NT proBNP, procalcitonin and central venous pressure were independent risk factors for POAF in patients after cardiac surgery (both $P < 0.05$, **Tables 4** and **5**).

ROC curves analysis

As shown in **Figure 2** and **Table 6**, Analysis of ROC curve showed that AUC of NT-proBNP for predicting POAF after cardiac surgery was 0.714, AUC of procalcitonin for predicting POAF after cardiac surgery was 0.824, and AUC of central venous pressure for predicting POAF after cardiac surgery was 0.682, all of which had good predictive value. In addition, the cut off value for NT-proBNP, procalcitonin and central venous pressure were 3886.0 ng/L, 1.8 $\mu\text{g/L}$ and 15.2 mmHg, respectively. Compared with either NT-proBNP, procalcitonin or central venous pressure, the combination of these three indicators had higher AUC value.

Discussion

The occurrence of POAF may involve a variety of factors, including cardiac disordered structural foundation, inflammation and oxidative stress, electrolyte and internal environment and so on [11, 12]. About 35% to 50% of POAF usually occurs in 2nd to 5th day after cardiac surgery [13-15]. Clinical efforts to prevent and control POAF after cardiac surgery are facing significant challenges, and the results are not ideal.

Combined serum markers in POAF patients

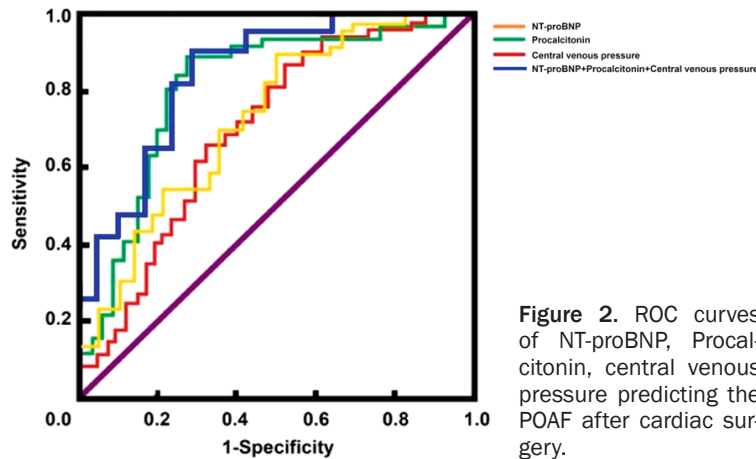


Figure 2. ROC curves of NT-proBNP, Procalcitonin, central venous pressure predicting the POAF after cardiac surgery.

Cardiac surgery leads to local inflammation around the heart and increased pericardial effusion. Postoperative pericardial fluid including blood, hemolysis of blood cells, hemoglobin, white blood cells and platelet activation markers are highly oxidized [16, 17]. Myocardia itself produces proinflammatory cytokines, resulting in local inflammation and directly alters cardiac function. Inflammation within the pericardial space may lead to myocardial electrical activity and apoptosis changes, cause elevated white blood cell count, and thus result in the formation of action potential heterogeneity and arrhythmia and dissemination [18, 19]. There are statistically significant differences between control group and POAF group in terms of procalcitonin and white blood cell count. Procalcitonin could reflect the activity of systemic inflammatory response. It was an independent risk factor for POAF in postoperative cardiac patients, indicating that the degree of inflammation caused by surgery was directly correlated with the incidence of POAF. Prevention of inflammation and pericardial effusion may be able to reduce the incidence of POAF, which was in consistent with previous results [20].

CVP is one of the hallmarks of volume load after cardiac surgery. NT proBNP is a polypeptide secreted by cardiac myocytes after increased load capacity. The load capacity was determined by the biological markers [21, 22]. It was reported that the cardiac function and prognosis in patients with heart failure could be evaluated through central venous pressure combined with NT proBNP [23-25]. Recent

studies showed that high volume could lead to increased intravascular volume and stimulate the right atrium diastole and left atrial enlargement. The elevated level of NT proBNP was closely associated with the degree of load capacity [26, 27]. Christians et al. [28] found that 88% of patients after a new atrial fibrillation had positive fluid balance. The study also found that patients with new-onset atrial fibrillation after cardiac surgery had liquid positive balance, elevated

central venous pressure and increased NT proBNP, compared with those in control group, indicating that increased NT-proBNP and elevated central venous pressure after surgery were the risk factors for POAF. These results were in accordance with the report by Bjerrum et al. [29].

There are some limitations in this study. First, this is a retrospective study, and there were no follow-up results. Second, the development of atrial fibrillation is involved in many factors. The parameters of this study was limited to age, gender, preoperative heart rate, mean arterial pressure, history of diabetes, history of hypertension, and history of coronary artery disease. Third, all patients' data were collected from this single center, which may lead to biased results.

In conclusion, the results of this study showed that NT-proBNP, procalcitonin and central venous pressure are closely related to atrial fibrillation after cardiac surgery. Joint detection of the three biomarkers has a better performance for predicting new-onset atrial fibrillation after cardiac surgery compared with each of the single factors, which may help clinicians make a preliminary judgment on such patients and offer a possibility of early intervention.

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Combined serum markers in POAF patients

Table 6. ROC parameters of NT-proBNP, Procalcitonin, central venous pressure for predicting the POAF after cardiac surgery

Indicators	AUC	95% CI	S.E	Sensitivity (%)	Specificity (%)
NT-proBNP	0.714	0.682-0.923	0.041	72.89	87.92
Procalcitonin	0.824	0.703-0.874	0.047	92.11	71.30
CVP	0.682	0.718-0.920	0.052	70.36	84.82
Combination of the above three indicators	0.914	0.642-0.911	0.049	94.82	80.75

Disclosure of conflict of interest

None.

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Combined serum markers in POAF patients

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