

The Effects of Risk Factors on Recovery of Elderly Patients With Atrial Fibrillation After Non-cardiac Surgery

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Research article

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Abstract

Background and Objective: Atrial fibrillation (AF) is one of the most common arrhythmias in clinical practice. However, no literature has reported the correlation between the quality of recovery of AF patients after non-cardiac surgery and their preoperative basic and intraoperative conditions. The present study aimed to screen factors that affect recovery of AF patients after non-cardiac surgery.

Methods: 120 patients with AF who aged ≥ 60 years old and scheduled to undergo non-cardiac surgery were included. The patients were divided into two groups according to the score of quality of recovery-15 (QoR-15) at 120 h after surgery, which were 122-150 points (satisfactory recovery, group A) and 0-121 points (poor recovery, group B). Their preoperative basic conditions (age, co-existing disease, mean ventricular rate, anticoagulant therapy, etc.), intraoperative conditions (the anesthesia satisfaction scale), and the QoR-15 scores after the surgery were recorded. Besides, the levels of plasma brain natriuretic peptide (BNP), high-sensitivity cardiac troponin (hs-cTn), and presepsin (soluble cluster-of-differentiation 14 subtype [sCD14-ST]) before and after surgery were measured. The data were analyzed to screen factors, influencing the postoperative recovery of patients with AF after non-cardiac surgery.

Results: The independent risk factors for elderly patients with AF after non-cardiac surgery were mean ventricular rate (odds ratio (OR): 1.085; 95% confidence interval (CI): 1.040-1.131; $P < 0.001$), high-risk surgery (OR: 0.185; 95% CI: 0.043-0.798; $P = 0.024$), and anesthesia satisfaction scale score (OR: 2.392; 95% CI: 1.524-3.753; $P < 0.001$). In the anesthesia satisfaction scale, hypotension ($P = 0.005$), tachycardia/bradycardia ($P = 0.021$), blood transfusion ($P = 0.047$), and RASS score ($P = 0.041$) were also found as risk factors for recovery. The levels of BNP and hs-cTn can be helpful to predict the prognosis in patients with AF.

Conclusion: Poorly controlled ventricular rate, high-risk surgery, and high score of anesthesia satisfaction scale can affect the prognosis in elderly patients with AF undergoing non-cardiac surgery. The levels of BNP and hs-cTn may correlate with early recovery of such patients.

Background

Atrial fibrillation (AF) is the most common arrhythmia diagnosed in clinical practice. In 2010, there were an estimated 33 million people worldwide with AF and this figure is expected to double by 2050 [1] {Chugh, 2014 #1;Chugh, 2014 #1}. AF-related cardiovascular events include cardiovascular death, heart failure, and stroke, accompanying with high morbidity and mortality [2]. Several studies have concentrated on the long-term survival rate and risk factors for patients with AF [3]. However, there is no report on the correlation between the quality of recovery (QoR) of AF patients after non-cardiac surgery and their preoperative basic and intraoperative conditions.

The risk of stroke in patients with AF is 5 times higher than that in non-AF patients, and it increases with age [4]. Antithrombotic therapy can prevent stroke and reduce the incidence of complications associated with AF [8]. However, the management of perioperative anticoagulation therapy is complicated, and the

risks among thromboembolism, stroke, and surgical bleeding must be weighed. To date, a limited number of scholars have studied the effects of preoperative anticoagulation on patients' early recovery.

It has been reported that the plasma brain natriuretic peptide (BNP) concentration can reflect the recovery of cardiac function in patients with AF [5]. The high-sensitivity cardiac troponin (hs-cTn) is also closely associated with the occurrence, development, and risk assessment of AF [6]. Presepsin is a humoral risk stratification marker for systemic inflammatory response syndrome and sepsis. Studies reported high level of presepsin in patients with acute heart failure and acute coronary syndrome without infection [7], and presepsin can be potentially a cardiac marker [8].

The present study aimed to screen out the risk factors for the postoperative recovery of patients with AF after non-cardiac surgery.

1. Methods

1.1 Patients

Patients with AF who underwent non-cardiac surgery under general anesthesia from May 2019 to May 2020 were included in this study. Ethical approval was obtained from the Ethics Committee of The First Affiliated Hospital of University of Science and Technology of China (USTC, China).

Inclusion criteria were as follows: (1) Patients' age \geq 60 years old; (2) Patients with history of elective non-cardiac surgery; (3) Patients who were diagnosed as permanent atrial fibrillation; (4) No cognitive impairment, no hearing impairment, no mental and neurological disorders.

Exclusion criteria were as follows: (1) Those requiring [second](#) surgery; (2) Patients who were allergic to the anesthetic drugs that should be used.

1.2 Methods

1.2.1 Preoperative test

Routine inspection: All patients underwent routine preoperative tests and cardiac evaluation, including dynamic electrocardiogram, chest X-ray, echocardiography, and laboratory examinations. Clinical assessment was performed by the same anesthesiologist preoperatively.

Patients' basic demographic characteristics were as follows: age, gender, body mass index (BMI).

Anticoagulation: It was attempted to indicate the necessity of performing anticoagulant treatment, the significance of utilization of other drugs preoperatively, left ventricular ejection fraction (LVEF), and applying CHADS₂ score for risk stratification for thrombotic events.

Cardiac ejection fraction, mean ventricular rate, high/medium risk of surgery, Goldman's cardiac risk index, New York Heart Association (NYHA) classification score, and American Society of

Anesthesiologists (ASA) physical status score. According to the 2007 American College of Cardiology/American Heart Association (ACC/AHA) guidelines, non-cardiac surgery with high-risk and medium-risk was defined, and low-risk non-cardiac surgery included endoscopy, biopsy, cataract surgery, and breast surgery. High-risk non-cardiac surgery involved the operation of massive blood loss in vascular surgery, or the operation that takes longer than 3 h [9].

1.2.2 Intraoperative test

Intraoperative monitoring included invasive arterial blood pressure, 5-lead electrocardiogram, pulse oxygen saturation, and partial pressure of carbon dioxide. The recorded data included grade of stainless steel used in surgery, name of surgery, type of anesthesia, duration of surgery.

Anesthetic satisfaction score was calculated with respect to existence of tachycardia during surgery, hypotension requiring booster maintenance, hypoxemia, hypothermia or hyperthermia, delayed resuscitation, the Richmond Agitation-Sedation Scale (RASS) after waking up, and utilization of analgesia pump. Tachycardia was defined as a ventricular rate greater than 100 beats/min, and hypoxemia was presented as arterial partial pressure of oxygen < 60 mmHg, or oxygen saturation < 90%, lasting for more than 5 min. Hypothermia was defined as body temperature < 36 °C, hyperthermia as body temperature > 37.5 °C, and delay in recovery as the time taken from complete cessation in anesthetic agent use was recorded as postanesthetic recovery time: patient is fully awake (regain consciousness and handshake); patient can move all 4 extremities voluntarily or on command; patient can freely perform deep breathing and can cough freely [10] (Table 6).

1.2.3 Follow up and grouping

QoR-15 scale was scored at 24 h preoperatively and at 24, 72, and 120 h postoperatively; additionally, the patient was followed-up by telephone at 30 days after surgery to indicate whether there were cardiovascular and cerebrovascular complications (cardiac failure and stroke). The patients were divided into two groups according to the score of QoR-15 at 120 h after surgery, which included 122-150 points (satisfactory recovery, group A) and 0-121 points (poor recovery, group B) [11].

1.2.4 Laboratory test

Blood sample (2 ml) was collected in the 1st day before and after surgery to monitor the concentrations of BNP, hs-cTn, and soluble presepsin. Blood was collected in 5-ml EDTA tubes and kept on ice no longer than 5 min before centrifugation at 3000 rpm for 15 min at 4 °C. Plasma was added into polypropylene tubes and stored at -80 °C for subsequent analysis. The above-mentioned indicators were measured by the double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) [BNP (NO20060514H), hs-cTn (NO20060509H), and presepsin (NO20060507H) were provided by Jiangsu Meimian Industrial Co., Ltd., Zhangjiagang, China]. The normal range of the these reagents was defined as follows: BNP (278.5-685.5 pg/ml), hs-cTn (688.42-1285.5 pg/ml), and (presepsin: 6.45-15.5 ng/ml).

1.3 Statistical analysis

Sample size: The events per variable (EPV) method was employed to calculate the sample size in the current study, that is the number of events for each independent variable, where events represent the category with a small number of dependent variables, EPV=10, to ensure accurate results[12]. It was confirmed that 120 cases reached the required sample size.

Statistical analysis was performed using SPSS 20.0 software (IBM, Armonk, NY, USA). Quantitative variables with normal distribution were presented as mean \pm standard deviation (SD) and analyzed using the Student's t-test, and the Wilcoxon rank-sum test was employed to analyze abnormally distributed variables. The chi-square test was used to compare count data. $P < 0.05$ was considered statistically significant. Univariate logistic regression analysis was utilized for significantly correlated variables, and independent risk factors were identified at $P < 0.05$.

2. Results

2.1 Follow-up and grouping

A total of 120 patients were enrolled and completed the follow-up. According to the score of QoR-15 scale at 120 h after surgery, they were divided into group A (satisfactory recovery, 50 cases) and group B (poor recovery, 70 cases).

2.2 Comparing patients' basic characteristics

There was no statistically significant difference between the two groups in gender, BMI (kg/m^2), ASA classification score, NYHA classification score, preoperative 24 h QoR-15 score, preoperative anticoagulation therapy, bridging anticoagulation, and CHADS₂ score ($P > 0.05$) (Table 1).

2.3 Comparing effective indicators

There were statistically significant differences between the two groups in age (≥ 75 years old) ($P=0.03$), high/medium risk of surgery ($P < 0.001$), the mean ventricular rate ($P=0.001$), Goldman's cardiac risk index ($P < 0.001$), and satisfaction score ($P < 0.001$) (Table 2).

2.4 Anesthesia satisfaction scale

The 13 indexes in the scaling system were analyzed, and it was found that there were significant differences between the two groups in terms of the following aspects: hypotension, tachycardia/bradycardia, and blood transfusion (Tables 3 and 4).

A total of 36 cases (72%) in group A had hypotension that needed to receive vasoactive drugs, of whom 16 cases (44.4%) were treated continuously. There were 64 cases (91%) in group B, of whom 42 cases (65.6%) were treated continuously. Patients who received vasoactive drugs were divided into two groups according to occasional and continuous use of vasoactive drugs, and the results showed that the

prognosis of the two groups was significantly different ($P=0.039$), and the group of occasional use of vasoactive drugs had better prognosis than the latter (Table 4).

In group A, tachycardia/bradycardia occurred in 23 cases (46%), of whom 6 cases were persistent (26.1%); in B group, there were 47 cases (67.1%), of whom 20 cases were persistent (42.5%). The patients with tachycardia/bradycardia during surgery were divided into two groups: occasional state and persistent state; the analysis showed that the prognosis of the two groups was not markedly different ($P=0.181$) (Table 4).

There were no patients with score of two points including both blood transfusion and RASS.

2.5 Independent risk factors

The above-mentioned five risk factors with significant statistical association were imported into the multivariate logistic regression analysis, and the results showed that mean ventricular rate (odds ratio (OR): 1.085; 95% confidence interval (CI): 1.040-1.131; $P<0.001$), high-risk surgery (OR: 0.185; 95% CI: 0.043-0.798; $P=0.024$), and anesthesia satisfaction scale score (OR: 2.392; 95% CI: 1.524-3.753; $P<0.001$) were independent risk factors influencing the recovery after non-cardiac surgery (Table 5).

2.6 Comparing the concentrations of BNP, hs-cTn, and presepsin

There was a statistically significant difference in the concentrations of BNP (preoperative $P=0.003$, postoperative $P=0.018$) and hs-cTn (preoperative $P=0.042$, postoperative $P=0.008$) at 24 h before and 24 h after surgery between the groups. There was no statistically significant difference in presepsin concentration between the two groups (preoperative $P=0.096$, postoperative $P=0.976$) (Table 6).

3. Discussion

A previous study showed that the postoperative hospitalization time in elderly patients is longer than that in general population, and the probability of postoperative complications is increased [13]. A number of scholars demonstrated that diabetes, coronary heart disease, intraoperative blood loss, and hemodynamic changes were independent risk factors for perioperative cardiovascular events in elderly patients [14]. Patients who aged over 60 years old were involved in this study, mainly because of low incidence (less than 1%) in the population who were younger than 60 years old, and the highest incidence of 12% was noted in the population who aged 75-84 years old [15]. The incidence of stroke in patients with AF who aged over 75 years old has significantly increased [36]; therefore, we divided the samples into two age-based groups—60-74 years old and ≥ 75 years old, and the results revealed that age was not an independent risk factor in the current study. In addition, we also used the Goldman cardiac risk index score to evaluate the patients' preoperative baseline, and the findings demonstrated that the two groups had no statistical significance, which is in disagreement with a previous research [14]. The reason for this discrepancy could be that senior patients with multiple diseases might be excluded before high-risk surgery. In the current study, among patients who aged 60-74 years old, the high-risk surgery accounted

for 29.2%, and among patients who aged 75 years old or more, the high-risk surgery accounted for 18.1%, further supporting our hypothesis.

The positive role of ventricular rate in preventing stroke complications in patients with AF has been previously reported [16]. However, few studies have concentrated on the relationship between preoperative ventricular rate and the prognosis of non-cardiac surgery in patients with AF. According to the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, the role of ventricular rate in patients with AF is 24 h dynamic electrocardiogram monitoring with an average heart rate ≤ 100 beats/min [17]. The patients in the current research had a ventricular rate of 77 ± 15 in group A, and 85 ± 11 in group B. We divided the patients into two groups with a ventricular rate of 80 as the demarcation point, and statistically analyzed their prognosis. The results revealed that there were statistically significant differences between the two groups ($P=0.002$), indicating that a stricter ventricular rate (≤ 80 beats/min) may be beneficial to the prognosis in such patients.

The incidence of perioperative cardiac events in the general population is only 1-2%. However, in patients with high-risk cardiovascular events, the morbidity and mortality of cardiac events remarkably increased [18]. In a previous research that included 1121 patients, the incidence of serious cardiac complications after high-risk, medium-risk, and low-risk non-cardiac surgery was 12.5%, 3.3%, and 1.1%, respectively [19]. Independent risk factors for postoperative cardiac events were myocardial infarction, emergency surgery, history of heart failure, and non-sinus heart rhythm [19]. Several previous studies have discussed the influence of high-risk surgery on the incidence of perioperative cardiac events, while few researches have concentrated on the influence of patients with AF. We hypothesized that in patients with AF as a group with high incidence of cardiovascular and cerebrovascular complications, high-risk surgery may be a risk factor that affects their prognosis. In the present research, patients with AF after high-risk surgery had lower recovery scores (OR: 0.185; 95% CI: 0.043-0.798; $P=0.024$), while 120 patients in this study did not have serious cardiac complications (requiring treatment) and death. This may be related to the point that the QoR-15 can indirectly reflect the existence of cardiovascular events, indicating no necessity to treatment (e.g., tachycardia, occasional arrhythmia, etc.).

The current study showed that the levels of BNP and hs-cTn were markedly different between the two groups 24 h before surgery and 24 h after surgery, and there was no significant difference in presepsin level. Several studies strongly suggested the use of troponin and BNP to predict the risk of non-cardiac surgery, in order to achieve the most reliable surgical results and prognosis [20, 21][Rodseth, 2010 #20;Devereaux, 2012 #19;Weber, 2013 #24], while few scholars have evaluated its predictive effect on AF patients' postoperative recovery. The findings of the present study also revealed that it has a satisfactory predictive value in patients' postoperative recovery with AF. Joint assessment of cardiac and inflammatory biomarkers (e.g., presepsin) may provide additional predictive data [22, 23]. Handke et al. [22, 23] reported that in patients with coronary heart disease undergoing non-cardiac surgery, elevation of presepsin level before surgery has a predictive effect on cardiovascular events 30 days after surgery. However, it was revealed that presepsin cannot predict the prognosis in such patients, and this may require further research with large sample size.

In the current research, anesthesia satisfaction scale score was found to be an independent risk factor for postoperative recovery in patients with AF (OR: 2.392; 95% CI: 1.524-3.753; $P < 0.001$). Because a number of factors during operation may have an impact on postoperative recovery, in order to reduce the interaction between multiple indicators, we scored anesthesia satisfaction, and integrated the intraoperative data, so as to be convenient for statistical analysis. The anesthesia satisfaction scale included tachycardia/bradycardia, hypotension maintained by vasoactive drugs, hypoxemia, hypothermia or hyperthermia, delayed awakening, RASS scale after awakening, and the use of analgesic pump after surgery. Based on the analysis of the role of each factor in the anesthesia satisfaction scale, it was found that there were significant differences in hypotension, tachycardia/bradycardia, blood transfusion, and RASS scale between the two groups. The intraoperative hypotension was herein defined as a change in mean arterial pressure by 20% as reported previously [24]. The results showed that the occurrence of hypotension in patients requiring vasoactive drugs during surgery might influence prognosis, and it was positively correlated with the length of stay at hospital ($P = 0.039$). A previous study also confirmed the authenticity of this outcome. A prospective multicenter study reported major perioperative cardiac and cerebrovascular events in 3387 patients, and found 7 independent risk factors, including intraoperative hypotension, intraoperative blood transfusion, etc. [25]. In another study, intraoperative hypotension (mean systolic arterial pressure < 40 mmHg) could predict cardiovascular events and postoperative complications [26]. In the present study, 23.3% of patients had RASS score $\geq +1$ (28 cases) which is higher than that reported by Card et al. [27], with incidence of 19% (in general population). The probability of postoperative agitation in AF patients is higher than that in the general population. Our results showed that postoperative RASS score could be a risk factor for the prognosis in patients with AF. The difference may be related to the point that RASS score and high-risk surgery are correlated together. Duration of high-risk surgery is longer, and incision pain and other factors may increase the probability of postoperative anxiety.

In the present study, no stroke occurred in all patients, and there was no significant difference in preoperative anticoagulant therapy or bridging anticoagulation and CHADS₂ score. The preoperative anticoagulation therapy and bridging anticoagulation in patients with AF remained controversial. The risk of stroke in patients with AF is 5 times higher than that in non-AF patients that gradually increases with age [4]. Antithrombotic treatment can prevent stroke and reduce the incidence of the associated complication [28]. However, the risk between thromboembolism, stroke, and surgical bleeding must be weighed. Observational studies have evaluated the timing and dose of low-molecular-weight heparin (LMWH) in the perioperative period [29, 30]. However, it is highly essential to indicate whether anticoagulation is essential in the perioperative period of warfarin anticoagulation. Due to the lack of evidence, the guidelines provided inconsistent recommendations on the necessity of anticoagulation [31-33]. A randomized, double-blind, controlled study of 1884 patients with AF showed that anticoagulant therapy was no less effective than LMWH in preventing arterial thromboembolism and reducing the risk of major bleeding, which is consistent with the results of the current study [34]. Therefore, it can be concluded that preoperative anticoagulation therapy and bridging anticoagulation do not necessarily

influence the prognosis in AF patients, and further attention should be paid to ventricular rate and intraoperative management.

This study contains a number of limitations. Firstly, the sample size was not large enough. Secondly, the qualifications of anesthesiologists and surgeons may also affect the prognosis in patients with AF, while the above-mentioned factors were not considered in the experimental design of this study.

4. Conclusions

In summary, we found that the independent risk factors for non-cardiac surgery in patients with AF were ventricular rate, high-risk surgery, and anesthesia satisfaction scale score. The preoperative anticoagulation therapy, bridging anticoagulation, and low CHADS₂ score showed to have no positive effect on the early recovery of AF patients. The detailed analysis of the anesthesia satisfaction scale score suggests that we need to pay close attention to intraoperative regulation, maintain hemodynamic stability during surgery, and reduce bleeding and blood transfusion. In addition, BNP and hs-cTn levels can predict the early recovery in patients with AF. Improving the QoR in patients with AF after non-cardiac surgery requires the joint efforts of anesthesiologists and surgeons.

Abbreviations

AF: Atrial fibrillation; QoR-15: The score of quality of recovery-15; BNP: Brain natriuretic peptide; hs-cTn: High-sensitivity cardiac troponin; sCD14-ST: Soluble cluster-of-differentiation 14 subtype; OR: Odds ratio; CI: Confidence interval; BMI: Body mass index; LVEF: Left ventricular ejection fraction; QoR: The quality of recovery; NYHA: New York Heart Association; ASA: American Society of Anesthesiologists; ACC/AHA: American College of Cardiology/American Heart Association; RASS: Richmond Agitation-Sedation Scale; EVP: Events per variable; SD: Standard deviation; AFFIRM: Atrial Fibrillation Follow-up Investigation of Rhythm Management; LMWH: Low-molecular-weight heparin; USTC: University of Science and Technology of China.

Declarations

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Not applicable.

Authors' contributions

Kai Zhang conceptualized, collected, and interpreted the clinical data, and wrote the manuscript. Xin Wei conceptualized, interpreted the clinical data, and revised the manuscript for important content.

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Availability of data and materials

The data supporting the results of this study can be obtained from the corresponding author upon reasonable request.

Ethics approval and consent to participate

We had obtained written informed consent from each participant and the study informant prior to the study. Ethical approval was obtained from the Ethics Committee of The First Affiliated Hospital of University of Science and Technology of China (USTC, China).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Characteristics of the study subjects				
Characteristic	A n = 50	B n = 70	t /c ² / W	P
Sex			0.024	0.877
Male	25	25		
Female	34	36		
BMI(kg/m ²)	23.74±3.49	22.63±3.50	1.718	0.088
ASA			4154	0.536
I	3	2		
II	40	60		
III	7	8		
NYHA cardiac classification			4200.5	0.781
I	1	2		
II	42	57		
III	7	11		
Anticoagulation yes/no	26/24	28/42	1.697	0.193
Bridging yes/no	32/18	54/16	2.481	0.115
EF	63.60±4.79	63.96±6.82	-0.337	0.737
Preoperative 24 h QoR-15 score	127.54±17.50	122.80±11.64	1.782	0.077
CHADS ₂	1.34±1.15	1.69±1.08	-1.677	0.096

Table 2 Univariates associated with recovery in patients with AF				
Characteristic	A n=50	B n=70	t / c ² / W	P
age(yr)			8.656	0.003
60-74	37	33		
≥75	13	37		
Ventricular rate (bpm)	76.94±14.52	85.03±10.75	-3.503	0.001
Golman score	11.82±3.08	13.79±2.10	-3.916	0.001
Satisfaction score	3.26±1.54	4.57±1.53	-4.625	0.001
High/Medium risk surgery			7.680	0.006
Medium risk surgery (n)	45	48		
High risk surgery (n)	5	22		

Table 3 Anesthesia satisfaction score 1				
Characteristic	A n=50	B n=70	c ² /t	P
Hypertension yes/no	29/21	41/29	0.004	0.95
Intubation yes/no	1/49	2/68	0.088	0.767
Vasoactive drugs yes/no	36/14	64/6	7.927	0.005
Tachycardia/Bradycardia yes/no	23/27	47/23	5.364	0.021
Length of operation yes/no	6/44	13/57	0.945	0.331
Blood transfusion yes/no	4/46	5/55	3.947	0.047
RASS score yes/no	7/33	21/49	4.174	0.041
Analgesic pump no/yes	24/26	35/35	0.047	0.829

Table 4 Anesthesia satisfaction score 2				
Characteristic	A	B	c ²	P
Vasoactive drugs (Occasionally/Continued)	20/16	22/42	4.243	0.039
Tachycardia/Bradycardia (Occasionally/Continued)	17/6	27/20	1.793	0.181

Table 5 Multivariate logistic regression

Variable	P	OR	95% CI
High/Medium risk surgery	0.024	0.185	0.043-0.798
Ventricular rate	0.001	1.085	1.040-1.131
Anesthesia satisfaction score	0.001	2.392	1.524-3.753

Table 6 Laboratory examination				
Laboratory examination	A n = 50	B n = 70	t	P
24h before operation				
BNP1 (pg/mL)	640±132	716±134	-3.085	0.003
hs-cTn2(pg/mL)	1673±343	1812±390	-2.061	0.042
Presepsin3(ng/mL)	14.6±3.1	13.5±3.6	1.679	0.096
24h after operation				
BNP (pg/mL)	394±119	444±109	-2.399	0.018
hs-cTn (pg/mL)	1168±249	1132±374	-2.707	0.008
Presepsin (ng/mL)	8.3±3.3	8.3±3.2	0.03	0.976
1.Normal range 278.5-685.5pg/mL; 2.Normal range 688.42-1285.5pg/mL; 3.Normal range 6.45-15.5ng/mL				