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Perfusion 2012 27: 504 originally published online 16 July 2012
DOI: 10.1177/0267659112454155

Perfusion

Perfusion
27(6) 504–511

DOI: 10.1177/0267659112454155
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The role of procalcitonin and N-terminal pro-B-type natriuretic peptide in predicting outcome after cardiac surgery

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Abstract

Objective(s): Determine the thresholds of procalcitonin (PCT) and N-terminal pro-B-type natriuretic peptide (Nt-pro-BNP) associated with poor prognosis after heart surgery with CPB. *Design:* Prospective observational study. *Setting*: Academic Medical Center Habib Bourguiba. *Participants:* Adult patients consecutively operated for coronary or valve surgery with CPB, elective or semi-urgent. *Interventions:* Serum concentrations of PCT and Nt-pro-BNP were determined before and after CPB, in the fourth postoperative hour (H4) and every day during the first 4 days. Receiver-operating characteristic curves and cut-off values were used to assess the ability of these markers to predict length of intensive care unit (ICU) stay >3 days. *Measurements and Main Results:* Forty patients were included in the study. Systemic inflammatory response syndrome (SIRS) occurred in 35 (87.5%) patients. Seventeen of them (42.5%) showed severe SIRS. Significantly higher serum concentrations of Nt-pro-BNP and PCT were found in patients with severe SIRS. Receiver operating characteristic (ROC) analysis showed that the threshold of PCT was 0.737 ng/mL and that of Nt-pro-BNP was 1235 pg/mL on day 1 could predict an ICU stay of more than 3 days. The association of Nt-pro-BNP to procalcitonin (p=0.009) better predicted the ICU stay than PCT alone (p=0.02) or Nt-pro-BNP alone (p=0.03). The best combination is Nt-pro-BNP + PCT + C-reactive protein (CRP) (p=0.007). *Conclusions:* PCT and Nt-pro-BNP on day 1 may be associated with severe SIRS and predict the length of stay. A biomarker approach combining PCT, CRP and BNP is superior to a traditional single marker for predicting ICU stay.

Keywords

pro-brain natriuretic peptide; procalcitonin; severe SIRS; ICU stay; heart surgery

Introduction

Systemic inflammatory response syndrome (SIRS) describes the clinical symptoms observed after various infectious and non-infectious insults. This generalized inflammatory response is common after coronary artery bypass grafting (CABG) and valvular replacement (VR) with or without cardiopulmonary bypass (CPB).[1,2] Factors such as surgical trauma, myocardial ischemia reperfusion, body temperature and cytokine cascade have been shown to induce SIRS after cardiac surgery with or without CPB.[3,4] This inflammatory cascade may result, for some patients, in severe postoperative complications, including renal, hepatic and neurological dysfunction, or respiratory and cardiovascular failure, thus, prolonging intensive care unit (ICU) stay.[3,5] Patients with SIRS associated with organ dysfunction can be classified as having severe SIRS.[6]

Brain natriuretic peptide (BNP) and its precursor N-terminal pro-BNP (Nt-pro-BNP) are cardiac hormones secreted by the ventricle which have recently been considered as effective markers of severity and prognosis of acute coronary syndromes[7,8] and heart failure.[9,10]

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Recent studies have found that postoperative BNP concentrations have an interesting prognostic value. Postoperatively elevated BNP levels are associated with prolonged intensive care unit (ICU) stay, occurrence of SIRS and severe SIRS and 1-year mortality after cardiac surgery with CPB.[11.12]

Procalcitonin is a propeptide of calcitonin produced by the thyroid gland[13] and is usually undetectable in the blood of healthy humans. It has been considered as one of the most effective markers of bacterial sepsis, providing a new tool for early diagnosis and prognostic assessment of infection in various clinical conditions.[14,15] Nevertheless, in cardiac surgery, the value of procalcitonin remains a matter of debate. Indeed, minor or moderate elevation of procalcitonin could be observed postoperatively because of surgical stress in the absence of any evidence of infection.[16,17] The PCT also seems to be a predictive marker of severe SIRS with organ dysfunction[2] and a prognostic marker.[18]

There is a need for markers with sufficient predictive value, especially with regard to short-term prognosis. The role of PCT and Nt-pro-BNP in predicting morbidity and mortality after cardiac surgery with CPB is not well understood. Thus, our objective was to determine the threshold of PCT and Nt-pro-BNP associated with poor prognosis after cardiac surgery.

Methods

Patient selection

After approval from the local ethics committee and written informed consent, 42 consecutive eligible patients (two patients died, leaving 40 [17 women, 23 men] in the study) undergoing cardiac surgery with cardiopulmonary bypass (CPB) were enrolled prospectively. All patients were free from active preoperative infection or inflammatory disease (leukocyte count <12,000/L, C-reactive protein [CRP] <5 mg/L, body temperature <38°C). Their preoperative medication did not include any antibiotic or corticosteroid. Inclusion criteria were: age >18 years and programmed or semi-urgent heart surgery under CPB. Patients with recent myocardial infarction (MI) <7days, preoperative renal or hepatic failure and infective endocarditis or documented infection within the last 7 days before surgery were excluded.

Anesthesia and surgery

Patients were premedicated with oral hydroxyzin (Atarax®)1 mg/kg, the night and 2 hours before surgery. After pre-oxygenation, intravenous anesthesia was induced with midazolam (Hypnovel® 0.1 mg/kg) and remifentanil (Ultiva® 1 g/kg within 1 min). Tracheal intubation was performed after adequate neuromuscular blockade with cisatracurium (Nimbex® 0.2 mg/kg). Anesthesia was maintained with remifentanil (0.2-0.4 g/kg/min), cisatracurium (0.1 mg/kg/h) and midazolam (0.05 mg/kg/h).

The patient's lungs were mechanically ventilated through an endotracheal tube, with the ventilator initially set to deliver an inspired fraction of oxygen of 0.5, tidal volume around 7 to 10 mL/kg, and a respiratory rate adjusted to maintain an arterial CO_2 pressure ($PaCO_{2)}$ between 35 and 40 mmHg. All patients were monitored by a 5-lead electrocardiogram, pulse oximetry, end-tidal carbon dioxide (capnography) and a systemic arterial catheter; right heart catheterization (pulmonary artery catheter) was used only when the preoperative left ventricular ejection fraction was <0.4. All patients received antibiotic prophylaxis with intravenous cefazol, 2 g before induction and 1 g every 4 hours during surgery, then every 8 hours for 24 hours in the case of CABG and 48 hours in the case of VR. Vancomycin, 1 g at induction and 1 g every 12 hours, was used in patients allergic to cefazolin or high-risk patients.

During surgery, the temperature was maintained with a warming blanket. After intravenous administration of heparin (300 IU/kg) and attaining an activating clotting time (ACT) greater than 400 seconds, CPB was initiated using an occlusive roller pump (Stockert S3, Stockert, Munich, Germany) and a membrane oxygenator with integrated arterial filter (Synthesis, Sorin, Mirandola, Italy). If the hematocrit is below 30% saline is replaced by 2 units of blood.

During CPB, pump flow was about 2.4 l/min/m^2 and the mean arterial pressure was maintained between 60 and 80 mmHg. Crystalloid cardioplegia was induced by infusing 1,000 mL of solution (4°C) with 80 mmHg aortic root pressure. For re-infusions, 250 mL of normal saline was used with the same pressure. At the end of surgery, intravenous (IV) protamine sulphate injection was administered to obtain an ACT <160s.

Blood samples

We performed seven blood samplings for each patient: the first one immediately after the induction of anesthesia and before CPB. The following samples were taken at the end of CBP (H0), 4 hours later (H4) and every day during the first four days (H24, H48, H72 and H96). Nt-pro-BNP was measured in each sample. Blood samples were collected from the radial artery and immediately centrifuged for 10 min. Plasma samples frozen at <20°C were stable for assays for >20 days after sampling, and all samples were analysed within 2 weeks.

Nt-pro-BNP and PCT determinations

Nt-pro-BNP concentrations were measured with a sandwich immunoassay, using polyclonal antibodies that recognize epitopes located in the N-terminal part (1–76) of pro-BNP (1–108). An electrochemiluminescence immunoassay was performed using an Elecsys analyser (Roche Diagnostics, Mannheim, Germany). The intra-assay coefficients of variation were 2.7% (at 175 pg /mL) and 1.9% (at 1068 pg /mL) and the inter-assay coefficients of variation were 3.2% (at 175 pg/ mL) and 2.6% (at 1068 pg /mL). The PCT concentrations in serum were measured by immunoluminometric assay with the commercially available LUMI test PCT (Brahms Diagnostica, Berlin, Germany). The inter-assay precision of the kit was 6–10%; the lower limit detection was 0.1 ng/mL.

Definitions of SIRS and severe SIRS

After surgery, microbiological and radiological examinations were performed daily until ICU discharge. SIRS was defined according to the classification of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference. The diagnosis of SIRS is held as the association of two of the following criteria: temperature >38°C or <36°C, WBC >12000/mm^3 or <4000/mm^3, tachypnea >20 breaths/min or hypocapnia <32 mmHg, postoperative organ dysfunction. The criteria for defining these organ dysfunctions were obtained from the Fagon et al. study.[6] SIRS classification was performed on all patients on the first postoperative day and every day during the first 4 postoperative days.

Infection status

Before and after the operation, body temperature and radiological examination were assessed daily until ICU discharge. Microbiological examinations of sputum, blood and urine were requested in case of infection or if bacteremia or sepsis was suspected.

Statistical analysis

Statistical analysis was performed with the software Statistical Package for Social Sciences (SPSS) for Windows (version 11.0, SPSS Inc., Chicago, IL). Quantitative variables were expressed as mean ± SD or median [minimum-maximum], depending on the nature of the distribution. Qualitative variables were expressed as frequencies. For the comparison of means, we used Student's t-test or the Mann-Whitney U test whenever the normality of the distributions was not observed (non-Gaussian distribution) or the size of one of the groups was small (<10). Categorical variables were analyzed by the $\chi 2$ test or Fisher's exact test whenever a population was <5. Differences between results were considered significant at a value of $p<0.05$. For multiple comparisons we used the Bonferroni correction.

In order to see the power of the different biomarkers in the prediction of ICU stay, we used linear regression to calculate predicted length of stay by each marker and we compared the predicted stays with the observed one.

To determine the different threshold values, we used the ROC (receiver operating characteristic). The best threshold value is the value having the best sensitivity and specificity.

Results

Forty-two patients were included in the study. Two patients were excluded due to their death at the first postoperative day. The remaining patients were divided into 23 CABG and 17 VR. The preoperative characteristics of the 40 patients are shown in Table 1.

SIRS developed in 35 patients (87.5%) and severe SIRS was seen in 17 patients (42.5%).

Mean age, body weight and body mass index (BMI) were similar between the groups: SIRS, severe SIRS and without SIRS. The Parsonnet score and EuroSCORE were also similar between the groups. The group of patients with severe SIRS, had a significantly prolonged duration of CPB, aortic cross-clamping and surgery. They also required more catecholamines. Duration of tracheal intubation and duration of stay were significantly longer in patients with severe SIRS compared with those without organ dysfunction or without SIRS (Table 2)

Median Nt-pro-BNP concentrations increased from 222 (20-2421) pg/mL preoperatively to 1534 (283-8201) pg/mL on postoperative day 1 ($p<0.001$). The levels of Nt-pro-BNP were significantly increased in patients with severe SIRS from day 1 postoperatively. Among patients without SIRS and those with SIRS without organ dysfunction, the levels of Nt-pro-BNP showed no significant difference (Table 3).

PCT concentration increased immediately after CPB to reach its peak on day 1 (1.7 ± 1.2 ng/mL) and then declined rapidly to day 2, day 3 and day 4 postoperatively. The rise in PCT concentration was significantly greater in patients with severe SIRS than in the other patients from the fourth hour after surgery up to the fourth postoperative day. No significant difference was detected between patients with simple SIRS and those without SIRS. In patients without SIRS, PCT levels did not exceed 0.5 ng/ml (Figure 1).

Patients staying longer than 3 days in the ICU showed significantly increased rates of Nt-pro-BNP from D1 to D3 : 2161 (1640.2) pg/mL, $p=0.03$ at Day 1; 2988 (2917.2) pg/mL, $p=0.02$ at Day 2 and 2566 (1396.7) pg/mL, $p=0.03$ at Day 3. The analysis of the receiver-operating characteristic (ROC) curve of Nt-pro-BNP for the prediction of ICU stay longer than 3 days has revealed that the Nt-pro-BNP rates on H24 and H48 have the best area

Table I. Demographics data and co morbidities.

	Study population (n=40)	Coronary surgery (n= 23)	Valvular surgery (n= 17)
Quantitative Variables : mean ± SD			
Age (years)	56.1 ± 14.9	61.8 ± 10.1	48.4 ±17 *
BMI (kg/m²)	24.3 ± 4.4	25.4 ± 4.7	22.8 ± 3.7
EuroSCORE (points)	4.07 ± 2.04	3.7 ± 1.8	4.7 ± 2.2
Parsonnet Score	7.7 ± 5.4	5.7 ± 4.8	10.8 ± 5.4 *
Qualitative Variables: number (%)			
Male	23 (57.5)	15 (65.2)	8 (47)
Female	17 (42.5)	8 (34.8)	9 (53)
Hypertension	15 (37.5)	11 (47.8)	4 (23.4)
Diabetes	12 (30)	9 (39)	3 (17.6)
COPD	3(7.5)	2 (8.7)	1 (5.9)
LVEF<50	4 (10)	3 (13)	1 (5.9)
Dyslipidemia	7 (17)	5 (21)	2 (11.7)
preop AF	2 (5)	0	2 (11.7)
MI <3 mois	11 (27)	11(47.8)	0

SD : standard derivation; *: Significant difference; BMI: body mass index; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; Preop AF: preoperative atrial fibrillation; MI: myocardial infarction .

Table 2. Pre-, intra- and postoperative data according to the presence and severity of SIRS

	Without SIRS n=5	SIRS n=18	Severe SIRS n=17
Age (years)	52.2 ±12.9	52.5± 16	61.2 ± 13.4
BMI (kg/m²)	28 ±9	24 ±3.3	23.3 ± 3.7
Parsonnet Score	5.6 ±3.3	7.05 ± 4.2	9.2 ± 7.01
EuroSCORE	2.8 ±1.9	4.05 ± 1.69	4.5 ± 2.3
Duration of CBP (min)	81.8 ±41.3	86.2 ± 25.4	114.7 ± 24.9 *
Duration of AC (min)	58.8 ±29.1	58.2 ± 25.4	79.1 ± 21.6 *
Duration of assistance (min)	23.2 ±14.8	25.6 ± 14.2	34.6 ± 10.9
Duration of surgery (min)	254 ±61	248 ± 40.6	294 ± 57.5 *
Extubation (hours)	2.6 ± 0.5	2.9 ± 0.8	5.2 ± 4.8 *
Duration of noradrenaline (days)	0.8 ±0.8	1 ± 0.7	2.1 ± 1.6 *
Duration of dobutamine (days)	0.2 ± 0.4	0.11 ±0.32	0,.9 ± 1.09 *
Duration of stay (days)	3.4 ±0.8	3.6 ± 0.9	7.8 ± 6.2 *

*: significant difference.
The variables are expressed as mean ± standard deviation
BMI: body mass index; CPB: cardiopulmonary bypass; AC: aortic cross-clamping.

under the curve and, for a « cut-off » of 1235 pg/ml measured at D1 after surgery, Nt-pro-BNP had a sensitivity of 74% and a specificity of 64% in predicting an ICU stay longer than 3 days with the area under the curve (AUC)=0.805.

The analysis of the receiver-operating characteristic (ROC) curve of PCT related to the different times for the prediction of ICU stay >3 days has revealed that the PCT rates on H24 and H48 have the best area under the curve and, for a threshold value of 0.737 ng/ml measured on Day 1, the PCT has a sensitivity of 76% and a specificity of 91% for predicting an ICU stay longer than 3 days with AUC=0.818 (Table IV). For a threshold value of 0.431 ng/ml measured on the 2nd postoperative day, the PCT has a sensitivity of 81% and a specificity of 82%.

Stay in the ICU predicted by each biomarker alone or with the association of different markers calculated by linear regression are summarized in Table 5. The association of Nt-pro-BNP to PCT (p = 0.009) predicted better stay in the ICU than PCT alone (p=0.02) or Nt-pro-BNP alone (p=0.03). The best combination is Nt-pro-BNP, PCT and CRP (p=0.007). One patient died on the 30th

Table 3. NT-pro-BNP levels according to the presence and severity of SIRS

Time	Without SIRS (pg/ml)	SIRS (pg/ml)	Severe SIRS (pg/ml)
Pre CPB	146 [53-419]	237 [20-748]	137 [20-1877]
H0	96 [28-716]	157 [20-614]	113 [20-2421]
H4	122 [60-468]	298 [28-1040]	325 [45-3630]
H24	955 [408-1616]	1035 [472-1709]	2291 [1607-8201]*
H48	1133 [351-1490]	880 [346-1818]	2876 [2203-13710]*
H72	943 [227-1209]	1031 [229-1810]	2292 [1676-11695]*
H96	609 [310-1609]	1151 [204-2233]	2332 [1109-5505]*

Pre CPB: before cardiopulmonary bypass.
The variables are expressed as mean with [limits]
*: significant difference.

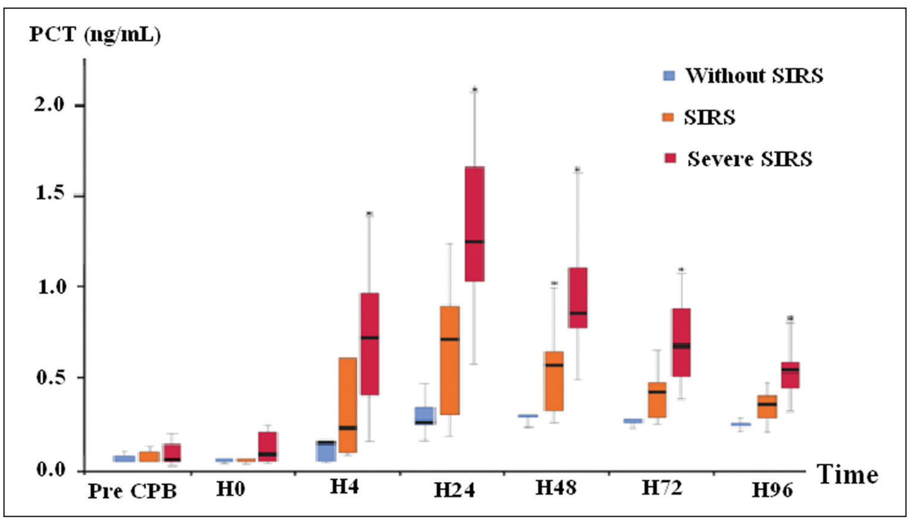

Figure 1. Levels of PCT according to the presence and severity of SIRS.

Table 4. Sensitivities, specificities for threshold values of procalcitonin and areas under the curve (AUC) for predicting an ICU stay >3 days at the different times studied.

Time	AUC	Threshold (ng/ml)	Sensibility (%)	Specificity (%)
H4	0.734	0.191	76	73
H24	0.818	0.737	76	91
H48	0.823	0.431	81	82
H72	0.749	0.295	76	73

Table 5. ICU stay predicted by each biomarker alone or in combination, and correlation with ICU stay observed.

marker	Predicted stay (PS)	Observed stay (OS)	Correlation SP-SO
PCT	4.7±0.84	5.4±4.6	r=0.360 p=0.02
Nt-pro-BNP	5.4±1.20	5.4±4.6	r=0.343 p=0.03
PCT + Nt-pro-BNP	4.7±0.96	5.4±4.6	r=0.414 p=0.009
PCT + Nt-pro-BNP + CRP	4.7±0.99	5.4±4.6	r=0.425 p=0.007

The variables are expressed as mean ± standard deviation;
r =.correlation coefficient

postoperative day following a septic shock. Thus, the study of mortality was not possible because of the low death rate in this study.

Discussion

Few studies are interested in examining the role of N-BNP and procalcitonin as early markers of severe systemic inflammatory response and length of ICU stay after cardiac surgery (valve replacement and coronary artery bypass grafting). We found that postoperative severe SIRS and ICU stay >3 days are associated with significantly higher serum N-BNP and PCT concentrations.

Cardiovascular surgery with extracorporeal circulation may cause a systemic inflammatory response syndrome (SIRS).[2,19] This generalized inflammatory response is common after cardiac surgery with cardiopulmonary bypass (CPB).[3,20] Besides infectious complications, many non-infectious factors could explain the development of a post-CPB inflammatory reaction. Factors such as blood exposure to non-physiological surfaces, surgical trauma, myocardial ischemia-reperfusion, changes in body temperature and endotoxin release have been shown to induce SIRS.[20] CPB has been shown to induce complement and leukocyte activation and the release of many inflammatory mediators.[21] This inflammatory cascade may cause severe postoperative complications in some patients, including renal and neurological dysfunction, altered liver function, or respiratory and cardiovascular failure.[22,23] SIRS associated with organ dysfunction, such as pulmonary or cardiovascular failure, has been classified as severe SIRS. Using the definitions given by the Consensus Conference of the American College of Chest Physicians/Society of Critical Care Medicine, we found that SIRS occurred in 87.5% of our patients. The incidence of SIRS is higher than that reported in previous studies after cardiac surgery with cardiopulmonary bypass, such as the Kerbaul et al.,[2] the Hensel and al.,[24] and the Boeken et al.[25] (36.5%, 47%, 50%, respectively), and the incidence of severe SIRS is also higher at 42.5% in comparison with the Kerbaul et al.[2] study (11%) and the Hensel et al.[24] one (22%).

PCT has been suggested as a specific marker of the severity of sepsis and infection.[26,27] High serum concentrations of PCT have been found in SIRS associated with severe burns[28] or after trauma.[29] Hyperprocalcitonemia has been associated with the early development of pulmonary or cardiovascular complications after cardiopulmonary bypass.[24,30] In a recent study, Kerbaul et al.[2] have shown that hyperprocalcitonemia was related to non-infectious postoperative severe SIRS associated with organ dysfunction after coronary artery bypass graft surgery.

Nt-pro-BNP has been proposed recently as an effective marker of the severity and prognosis of acute coronary syndromes[7,8] and congestive heart failure.[31,32] The mechanism of production of BNP is unclear; low preoperative left ventricular ejection fraction (LVEF), associated with subacute preoperative myocardial ischemia, may increase regional ventricular wall stretch due to local depression of myocardial contraction.[8] Mechanical stretch could, therefore, stimulate N-BNP secretion and increase messenger RNA expression of IL-6 and cardiotrophin I, a cytokine of the IL-6 family.[33] However, IL-6 concentrations are also raised in cardiac surgery without CPB and could be involved in the cytokine cascade after surgery.[4] It is interesting to investigate the role of PCT and N-BNP as markers of severe SIRS after cardiac surgery with CPB. The normal range of serum PCT concentrations after cardiac surgery with CPB is not yet clearly defined. Aouifi and colleagues[1] showed that PCT concentrations increased after surgery, irrespective of the type of cardiac surgery, with a peak on the first postoperative day. In our study, postoperative changes in PCT concentrations were delayed. Over the 3 days after surgery, PCT concentrations remained <0.5ng/ml in patients without any complications, including patients with SIRS, but without any organ dysfunction.

These results are close to those reported by Kilger and colleagues[34] (0.7 ng/ml) who clearly showed that procalcitonin was a marker of systemic inflammatory response after cardiac surgery. All patients who developed organ dysfunction had a significantly increased PCT concentration from 4 h after surgery, which peaked on the first postoperative day.

Unlike PCT, few studies have examined the place of Nt-pro-BNP in the diagnosis of severe SIRS after cardiac surgery. In our study, rates of Nt-pro-BNP were significantly greater in patients with severe SIRS, starting from the first day. For patients without SIRS and those with SIRS without organ dysfunction, the rates of Nt-pro-BNP showed no significant difference. Our results are aligned with those of Kerbaul and al.[2] which showed that severe SIRS with cardiovascular dysfunction has been associated with high rates of Nt-pro-BNP after off-pump coronary artery surgery. In our study and that of Kerbaul and al.,[2] the rates of Nt-pro-BNP correlated with greater use of positive inotropic drugs (dobutamine). This reflects the myocardial failure in these patients.

In our study, the PCT levels on day 1 correlated with length of stay in ICU. This result is consistent with that of Meisner et al.[30] who conducted a study with a study population larger than the ours (208 patients receiving CABG or VR with CPB). In addition, patients staying longer than 3 days in the ICU showed significantly increased rates of Nt-pro-BNP from day 1 to day 4. This is consistent with the results of Crescenzi et al.[35] which showed that postoperative levels of Nt-pro-BNP are associated with an ICU stay longer than four days after CABG.

Conclusion

PCT and Nt-pro-BNP levels on day 1 may be associated with severe SIRS and it can correlate with length of ICU stay of more than 3 days, with respective thresholds 0.737 ng/mL and 1235 pg/mL. A biomarker approach, combining PCT, CRP and BNP, was superior to a traditional single marker for predicting ICU stay.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of Interest Statement

None declared.

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