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Procalcitonin and white blood cells, combined predictors of infection in cardiac surgery patients

María Heredia-Rodríguez, MD, PhD,[a,b] *Juan Bustamante-Munguira, MD, PhD,*[c,*] *Mario Lorenzo, MD,*[b] *Esther Gómez-Sánchez, MD,*[a,b] *F. Javier Álvarez, MD, PhD,*[d] *Inmaculada Fierro, MD, PhD,*[d] *Esther Conejo, MD, PhD,*[a,b] *and Eduardo Tamayo, MD, PhD*[a,b]

[a] *BioCritic. Group for biomedical Research in Critical Care Medicine, Valladolid, Spain*
[b] *Department of Anesthesiology and Surgical Critical Care, Hospital Clínico Universitario de Valladolid, Valladolid, Spain*
[c] *Department of Cardiovascular Surgery, Hospital Universitario de La Princesa, Madrid, Spain*
[d] *Department of Pharmacology and Therapeutics, Valladolid University Physicians College, Valladolid, Spain*

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ABSTRACT

Background: Sepsis is strongly associated with an increased risk of postoperative mortality, longer length of hospital stay, and elevated health care costs. Early clinical symptoms overlap with those of systemic inflammatory response syndrome, a response that commonly occurs after cardiac surgery with cardiopulmonary bypass. Since a combination of biomarkers has been demonstrated to improve the prediction of postoperative infection, the objective of the present study was to test whether the combination of C-reactive protein (CRP), white blood cells (WBC), and procalcitonin (PCT) is able to predict postoperative infection in a large cohort of cardiac surgery patients.

Material and methods: Case-control study involving 423 patients who underwent cardiac surgery with cardiopulmonary bypass. Patients were retrospectively classified into two groups based on whether they developed severe sepsis or septic shock during the postoperative period. Blood samples for biological measurements (PCT, CRP, and WBC) were drawn on the first day in the intensive care unit, then once daily in the morning until the 10th postoperative day.

Results: CRP median values were similar in both groups. WBC and PCT median values were significantly higher in patients with infection than without during the first 10 postoperative days. With elevation cutoffs $\leq$3 times (OR: 4.058; 95% CI: 2.206-7.463; $P = 0.001$) and $\geq$4 times (OR: 10.274, 95% CI: 3.690-28.604; $P < 0.001$), the median value for PCT (1.7 ng/mL) and/or WBC (13,000 cells/mm^3) on the second postoperative day was significantly associated with the development of infection.

Conclusions: The goal of this study was to use a large cohort of cardiac surgery patients to ensure that the results were representative of this population. The combination of PCT and WBC levels over the first three postoperative days was able to predict postoperative infection within the 30 d following cardiac surgery.

* *Corresponding author*: Department of Cardiovascular Surgery, Hospital Universitario de La Princesa, Madrid, Spain. Tel.: +34 915202268; fax: +34 915202201.
E-mail address: jbustamantemunguira@gmail.com (J. Bustamante-Munguira).
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Introduction

Sepsis is one of the most frequent causes of admission to the intensive care unit (ICU) worldwide.[1] Sepsis has been defined as a systemic inflammatory response caused by an infection; however, bacteremia is only identified in approximately one-third of patients with sepsis.[2,3] Fever, leukocytosis, and tachycardia are early clinical symptoms of sepsis that overlap with symptoms of systemic inflammatory response syndrome (SIRS) of noninfectious origin, a response that commonly occurs after cardiac surgery with cardiopulmonary bypass (CPB).[4] Sepsis has been strongly associated with an increased risk of postoperative mortality, longer length of hospital stay, and elevated health care costs.[5,6] Therefore, the identification of a biomarker able to predict sepsis in surgery patients and to differentiate infectious and noninfectious SIRS has become an issue of great importance.

Procalcitonin (PCT) is one of the inflammatory mediators involved in SIRS and is being evaluated as a biomarker for sepsis and infection in postoperative patients.[7,8] Although most studies have demonstrated the usefulness of PCT as a biomarker of infection,[9–11] other studies have not.[12,13] Elevated white blood cell (WBC) count has traditionally been another predictor of infection in clinical practice, although it has also been shown to increase after cardiac surgery with CPB.[14,15] Likewise, elevations in C-reactive protein (CRP) levels have also been associated with postoperative infection and sepsis.[16] Several studies have established cutoff points for CRP at 5-10 mg/dL.[17] Despite the existence of a number of studies evaluating the use of PCT as a marker of infection, these were all conducted using small cohorts of cardiac surgery patients.[9–11] Since the combination of biomarkers has been shown to improve the prediction of postoperative infection, the objective of the present study was to test whether the combination of CRP, WBC, and PCT is able to predict postoperative infection in a large cohort of cardiac surgery patients.

Material and methods

A case-control study was designed, including patients aged ≥18 y who underwent a cardiac surgery with CPB at the Hospital Clínico Universitario of Valladolid (Spain) between January 2011 and 2015. A total of 2,198 patients were screened since the beginning of the study. The case group consisted of all patients who developed severe sepsis or septic shock ($n = 122$, infection rate: 5.5%; 94 with pneumonia and 28 with surgical site infection); in the control group, patients from 2014 that did not develop these conditions were included consecutively ($n = 301$). The predicted ratio of patients with and without infection was estimated at 1:3. All patients that began receiving antibiotic treatment for suspected infection whose germ culture results were negative were excluded from the study. Exclusion criteria were as follows: having a clinically detectable preoperative infection, use of corticosteroids within 1 wk before surgery, and death within the first 48 h after surgery. All patients received prophylactic antibiotic treatment with cefazolin, 1 g every 8 h, during the first 24 h after surgery. The study was approved by the Institutional Review Board and conducted in accordance with the guidelines established by the hospital's Ethics Committee and the Declaration of Helsinki.

Definitions and laboratory methods

Diagnoses of SIRS, sepsis, and septic shock were established according to guidelines from the American College of Chest Physicians/Society of Critical Care Medicine consensus.[18] It was an indispensable condition that every patient with sepsis and septic shock had germ-positive cultures. The diagnosis of nosocomial pneumonia was considered with Clinical Pulmonary Infection Score greater than 6 and microorganism isolation.[19] Definitions for nosocomial surgical site infections (SSI) were in accordance with CDC guidelines.[20] The final diagnosis of infection (pneumonia, SSI), SIRS, sepsis, and septic shock was determined by two independent experts who were blinded to PCT levels, and in cases of disagreement, consensus was reached by means of a third expert. Microorganisms were isolated from the sputum and/or surgical wounds of patients with infection on the day of infection diagnosis and on each subsequent day until cultures were negative or sepsis evolved. Blood samples for biological measurements (PCT, CRP, and WBC) were drawn on the first day in the ICU, then once daily in the morning until the 10th postoperative day. PCT levels were measured using an immunoluminometric assay (LUMItest Procalcitonin; Brahms Diagnostica, Berlin, Germany) adapted to the 6000 Cobas analyzer (Roche Diagnostics, Roche Holding AG, Switzerland), showing a concentration range of 0.2-100 ng/mL.

Statistical analysis

Categorical variables were expressed as absolute and relative (%) frequencies, and continuous variables were expressed as the median and standard deviation. Baseline comparisons between the two groups were done using the chi-squared test for categorical variables and Student *t*-test or the Mann-Whitney *U* test for continuous variables. The development of a postoperative infection was analyzed by performing a logistic forward stepwise regression analysis (odds ratio [OR] and 95% confidence interval [95% CI]), adjusting for demographic and clinical factors. Variables introduced in the models showed a tolerance value higher than 0.4 or variance inflation less than 2.5, a condition number less than 10, and a variance of ≥2 no greater than 0.5. Collinearity was evaluated between the variables. The area under the curve (AUC) was calculated from receiver-operating characteristics (ROC) curves derived from regression models. The statistical significance was established for $P \leq 0.05$. All calculations were performed with SPSS 20.0 software.

Results

Demographic and clinical information are shown in Table 1, grouped according to the development or