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

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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.

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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

Table 1 – Demographic and clinical information of cardiac surgery patients regarding the development of a postoperative infection.

	No infection ($n = 301$)	Infection ($n = 122$)	P-value
Preoperative factors			
Age, mean years ± SD	65.9 ± 11.2	71.1 ± 9.5	<0.001
Sex male, *n* (%)	199 (66.1)	82 (67.2)	0.828
Hypertension, *n* (%)	168 (55.8)	79 (64.8)	0.091
Diabetes mellitus, *n* (%)	69 (22.9)	23 (18.9)	0.358
Obesity, *n* (%)	48 (15.9)	18 (14.8)	0.759
Alcohol drinking, *n* (%)	13 (4.3)	5 (4.1)	0.919
Hepatic disease, *n* (%)	8 (2.7)	4 (3.3)	0.728
Respiratory disease, *n* (%)	37 (12.3)	18 (14.8)	0.495
Chronic renal failure, *n* (%)	14 (4.7)	11 (9.0)	0.085
Intraoperative factors			
Emergency surgery, *n* (%)	17 (5.6)	38 (31.1)	<0.001
Type of surgery, *n* (%)			
Valve	96 (32.1)	26 (21.5)	0.03
CABG	152 (50.8)	60 (49.6)	0.81
Valve + CABG	51 (17.1)	35 (28.9)	0.006
Total CPB time, mean min ± SD	113.8 ± 46.1	142.7 ± 51.7	<0.001
Ejection fraction, *n* (%)	57.8 ± 11.1	51.8 ± 12.2	<0.001
Risk score			
SOFA score, mean points ± SD	5.7 ± 1.1	7.1 ± 2.2	<0.001
APACHE II score, mean points ± SD	10.5 ± 2.8	15.1 ± 3.8	<0.001
Postoperative factors			
Time to extubation, mean days ± SD	1.5 ± 5.6	21.7 ± 64.8	<0.001
Polytransfusion, *n* (%)	1 (0.3)	12 (9.8)	<0.001
Length of stay, mean days ± SD			
Preoperative hospitalization	9.52 ± 9.6	8.9 ± 10.3	0.591
Total in hospital	21.4 ± 16.4	51.1 ± 71.6	<0.001
In the ICU after surgery	3.9 ± 8.2	33.8 ± 90.9	<0.001
30-d mortality, *n* (%)	5 (1.7)	20 (16.4)	<0.001
Hospital mortality, *n* (%)	13 (4.3)	45 (36.9)	<0.001

SD = standard deviation; CABG = coronary artery bypass graft; SOFA = Sequential Organ Failure Assessment; APACHE II = Acute Physiology and Chronic Health Evaluation II.

avoidance of a postoperative infection. Patients were mainly male (67.2% *versus* 66.1%; $P = 0.828$), and the main comorbidity was hypertension (64.8% *versus* 55.8%). Emergency surgery was performed in more patients with infection (31.1%) than those without infection (5.6%; $P < 0.001$). Sequential Organ Failure Assessment and Acute Physiology and Chronic Health Evaluation II scores were higher in patients with infection (7.1 ± 2.2 points and 15.1 ± 3.8 points, respectively) than those without infection (5.7 ± 1.1 points and 10.5 ± 2.8 points; $P \leq 0.001$ for both). Hospital mortality was higher in patients with infection (36.9%) than in those without infection (4.3%; $P < 0.001$). A total of 156 microorganisms were isolated from patients with infection (Table 2). In 32 of the 94 patients with pneumonia, microorganisms were isolated from the surgical site, in addition to the lungs.

WBC, CRP, and PCT levels

Median WBC counts were significantly higher in patients with infection than in patients without infection, peaking on the third postoperative day in those with infection (Fig. 1). By contrast, the CRP median values were similar in both groups until approximately the seventh postoperative day. The PCT median values showed differences between patients with infection and those without infection during the first 4 d, with values being significantly ($P < 0.05$) higher in patients with infection. The WBC and PCT median values in patients with infection showed a steep increase within the first 3 postoperative days.

Table 2 – Description of pathogens isolated from patients with infection ($n = 122$).

Microorganism	Number of isolations from different locations		
	Lung (sputum)	Surgical site	Total
Acinetobacter spp.	11	4	15
Escherichia coli	1	8	9
Haemophilus influenzae	14	—	14
Klebsiella spp.	9	2	11
Pseudomonas aeruginosa	13	5	18
Enterobacter spp.	2	1	3
Other	10	5	15
Total of Gram-negative	60	25	85
Staphylococcus aureus	15	12	27
Methicillin-resistant	11	7	18
Methicillin-susceptible	4	5	9
Streptococcus pneumoniae	1	1	2
Staphylococcus epidermidis	13	13	26
Other staphylococcus	2	7	9
Enterococcus spp.	1	1	2
Others	2	3	5
Total of Gram-positive	34	37	71
Total pathogens	94	62	156

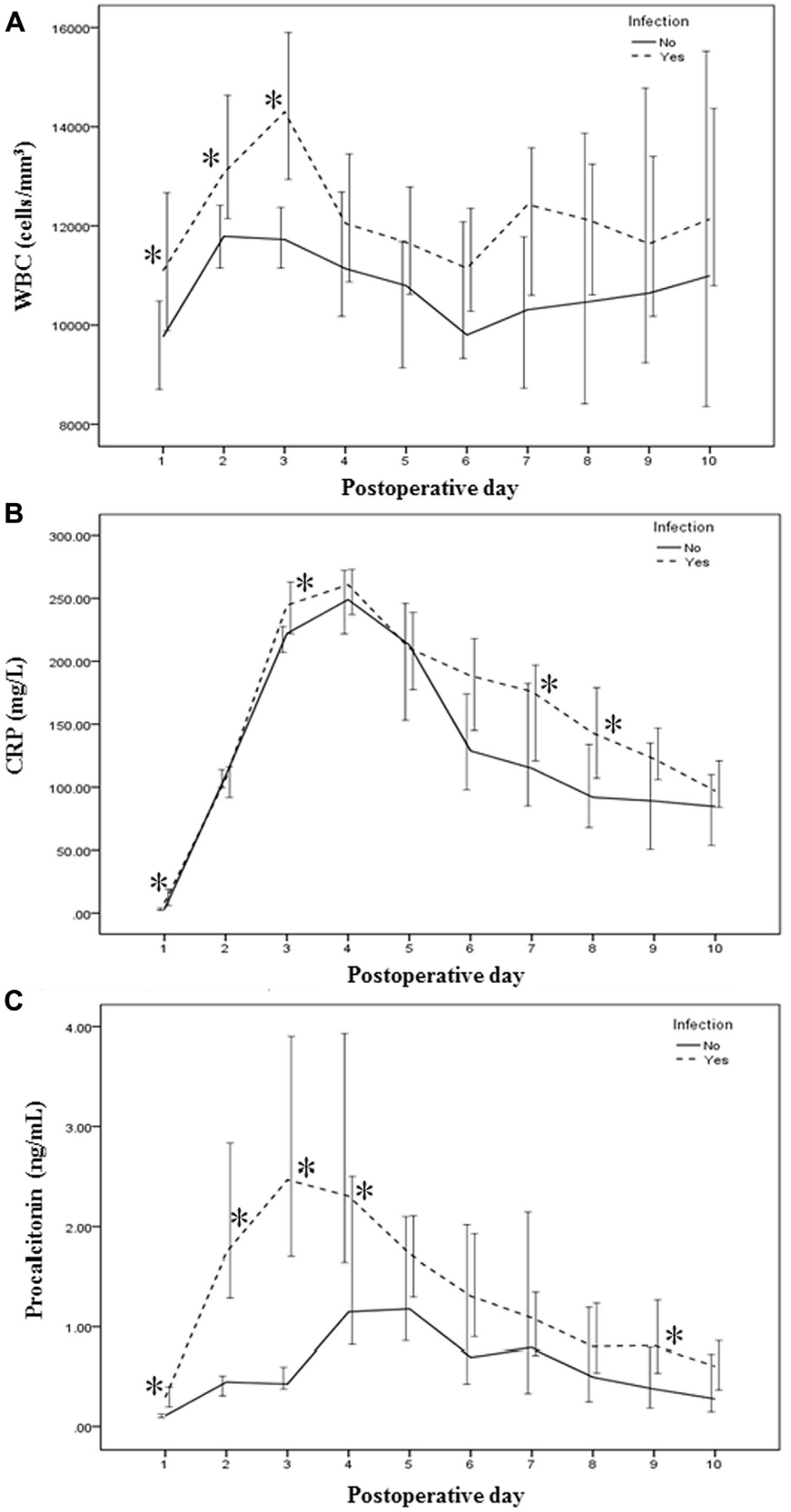

Fig. 1 – Evolution of white blood cell count (WBC, A), C-reactive protein (CRP, B), and procalcitonin (C) in patients with infection (dashed line) and those without infection (solid line) during the first 10 postoperative days. An asterisk represents the statistical differences between groups ($P < 0.05$).

Formulating the hypothesis

CRP was not included because it was not different between the two groups. Taking into account the differential WBC and PCT values during the first postoperative days, we chose the median values for PCT (1.7 ng/mL) and WBC (13,000 cells/mm^3) on the second postoperative day as representative cutoff points for predicting infection. We then proposed the following hypothesis to be tested: "The total number of times that PCT and/or WBC elevate from their representative cutoff points during the first 3 postoperative days could act as an adequate parameter for predicting postoperative infection". Assuming this hypothesis, there were six possible scenarios: (1) Either PCT or WBC elevates from its cutoff point on 1 d while the other did not (total number of times of elevations = 1); (2) both PCT and WBC elevate from their cutoff points on only 1 d or one of them exceeded its cutoff point on 2 d while the other did not (total number = 2); (3) either PCT or WBC elevates from its cutoff point on 2 d while the other elevates from its cutoff point on 1 d, or one of them elevates from its cutoff point on 3 d while the other did not (total number = 3); (4) both PCT and WBC exceeded their cutoff points on 2 d, or one of them elevates from its cutoff point on 3 d and the other on 1 d (total number = 4); (5) either PCT or WBC exceeded its cutoff point on 3 d while the other elevates from its cutoff point on 2 d (total number = 5); and (6) both PCT and WBC elevate from their cutoff points on 3 d (total number = 6).

Predicting postoperative infection

The total number of times that PCT and WBC elevate from their cutoff values (from 1 to 6, with 0 as reference) was initially evaluated in the regression model. The model, adjusted for age, ejection fraction, emergency surgery, and total CPB time, revealed that the number of elevations above the respective cutoff values within the first 3 postoperative days was significantly associated with the development of postoperative infection: [1 time (OR: 3.453), 2 times (OR: 3.649), 3 times (OR: 6.171), 4 times (OR: 9.696), and 5 times (OR: 13.431)].

The ROC curve showed an AUC of 0.845 (95% CI: 0.801-0.888). After performing the initial regression model and with the aim of facilitating the analysis, the total number of times was reduced to only two groups: elevation cutoffs ≤3 times and ≥4 times, i.e. the ≥4 group required that both PCT and WBC were "significantly elevated" (with respect to the representative cutoff points) for at least 2 d. When reduced to two groups, the independent factors associated with the development of an infection were elevation cutoffs ≤3 times (OR: 4.058; 95% CI: 2.206-7.463; $P = 0.001$), elevation cutoffs ≥4 times (OR: 10.274, 95% CI: 3.690-28.604; $P < 0.001$), age (OR: 1.051, 95% CI: 1.022-1.080; $P = 0.001$), ejection fraction (OR: 0.965, 95% CI: 0.942-0.988; $P = 0.003$), CPB time (OR: 1.009, 95% CI: 1.003-1.015; $P = 0.003$), and emergency surgery (OR: 4.434, 95% CI: 2.014-9.759; $P < 0.001$; Table 3). The ROC curve indicated an AUC for this model of 0.842 (95% CI: 0.798-0.886; Fig. 2).

Predicting 30-d mortality

Keeping the simplified model of only two groups (elevation cutoffs ≤3 times and ≥4 times), the independent factors associated with the development of 30-d mortality were elevation cutoffs ≤3 times (OR: 4.808; 95% CI: 1.378-16.780; $P = 0.014$), elevation cutoffs ≥4 times (OR: 5.879, 95% CI: 1.296-26.664; $P = 0.022$), CPB time (OR: 1.011, 95% CI: 1.003-1.018; $P = 0.007$), and emergency surgery (OR: 3.446, 95% CI: 1.132-10.494; $P = 0.029$; Table 4). The ROC curve indicated an AUC for this model of 0.835 (95% CI: 0.763-0.906; Fig. 3).

Table 3 – Regression model for identifying factors associated with the development of an infection within 30 postoperative days.

	Odds ratio	95% CI	P-value
Elevations ≤3 times	4.058	2.206-7.463	<0.001
Elevations ≥4 times	10.274	3.690-28.604	<0.001
Age	1.051	1.022-1.080	0.001
Ejection fraction	0.965	0.942-0.988	0.003
Cardiopulmonary bypass time	1.009	1.003-1.015	0.003
Emergency surgery	4.434	2.014-9.759	<0.001

Discussion

The most relevant findings of this study are: (1) the combination of PCT and WBC has been found to be a useful parameter for predicting postoperative infection, (2) the predictive factor is stronger when both PCT and WBC levels were significantly elevated for at least 2 d, and (3) elevation cutoffs ≤3 times and elevation cutoffs ≥4 times are considered good predictors of mortality. In our study, patients with no infection showed high CRP values during the first 5 postoperative

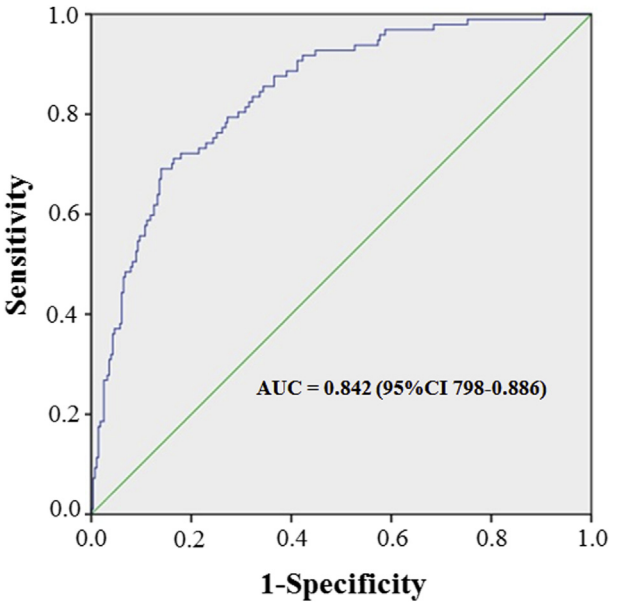

Fig. 2 – ROC curve representing the sensitivity and specificity of the model for predicting postoperative infection. AUC indicates the area under the curve. (Color version of figure is available online.)

Table 4 – Regression model for identifying factors associated with the 30-d mortality.

	Odds ratio	95% CI	P-value
Emergency surgery	3.446	1.132-10.494	0.029
Cardiopulmonary bypass time	1.011	1.003-1.018	0.007
Elevations ≤3 times	4.808	1.378-16.780	0.014
Elevations ≥4 times	5.879	1.296-26.664	0.022

days. This observation is supported by the literature, which states that CRP is involved in the acute phase reaction after surgery.[21] The median CRP value was significantly higher in patients with infection on the third postoperative day. A CRP peak above the 75th percentile on the third day has been shown to be associated with infection.[22] The significantly higher WBC and PCT levels in patients with infection found in our study are also supported by previous studies in cardiac surgery patients.[23,24] Despite the existence of a number of studies evaluating the use of PCT as a marker of infection, these were all conducted using a small cohort of cardiac surgery patients.[9–11]

One goal of our study was to evaluate the predictive use of PCT in combination with other biomarkers in a large cohort of these patients. A previous study conducted in cardiac surgery patients showed a moderate AUC value for PCT at 0.72 as a predictor of infection.[25] Two different studies have demonstrated that the AUC for the correlation of PCT with confirmed pneumonia in ICU patients was 0.51.[12,26] The only studies in adult patients showing PCT as a good marker of infection with high AUC values (0.92 and 0.87) were studies with very low numbers of patients with infection (20-38 patients).[10,11,27] Most previous studies have indicated that PCT alone does not aid in predicting the development of infection.[11,25,26,28] The cutoff value for PCT as a biomarker of infection ranges from 0.5-1.5 ng/mL.[9,29] Jebali *et al.* took the maximum value of each biomarker on the third postoperative day or later, using the ROC curve to identify the best cutoff value for each biomarker to diagnose infection. With a cutoff of 1.5 ng/mL, the AUC was 0.88, and the sensitivity and specificity were 0.93 and 0.80, respectively.[9] In our study, we chose the median value on the second postoperative day as the cutoff value for both variables. At 1.7 ng/mL, our PCT cutoff value was similar to the one used by Jebali *et al.*; however, our WBC cutoff value of 13,000 cells/mm^3 was higher (as compared to 12,000 cells/mm^3). In our study, we propose a prediction model based on the number of times that both WBC and PCT exceed a representative cutoff point during the first 3 postoperative days. In other words, we proposed that the combination of elevated levels of WBC and PCT may be useful for predicting postoperative infection. Indeed, our results indicated that exceeding the representative cutoff points for PCT and WBC >3 times, i.e. both PCT and WBC levels being significantly elevated for at least 2 d, resulted in 10 times higher risk for developing an infection within the 30 d following cardiac surgery compared to levels that did not exceed the cutoff points. This marker may be useful in the early differentiation of postoperative cardiac surgery patients at increased risk of developing an infection to start proper management early in the postoperative period and to differentiate between patients with sepsis and those with noninfectious SIRS.

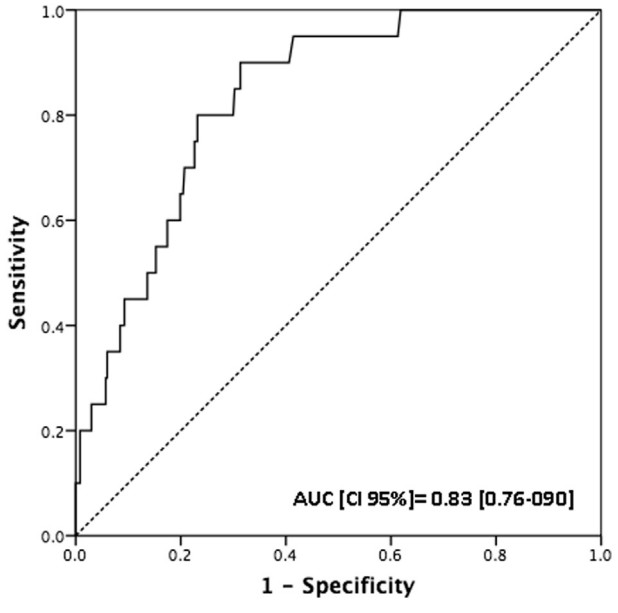

Fig. 3 – ROC curve representing the sensitivity and specificity of the model for predicting 30-d mortality. AUC indicates the area under the curve.

In our study, the duration of hospital and ICU stays were, as expected, significantly higher in patients with infection. These results are in agreement with previous studies.[10,29] Both 30-d and hospital mortality rates were significantly higher in patients with infection because sepsis is an important mortality risk factor.[30,31] Risk factors associated with 30-d mortality were emergency surgery, CPB time, elevations ≤3 times, and elevations ≥4 times. In our model, we have found that elevations ≤3 times and elevations ≥4 times are significant predictors of mortality.

The main limitation of the study was that data were obtained from a single institution; and therefore, may not be extrapolated to other settings. Although we agree that a multicentre study would reduce potential center-specific bias, we think that limiting data to a single center nevertheless presents several advantages, such as the inclusion of a homogeneous population of patients, adherence to consistent clinical routines, consistent quality of data, and consistent surgical quality over a period of time. Other limitations of the study were the prospective observational nature of the study, which did not allow us to select patients based on their demographic and clinical characteristics; therefore, running the risk of losing a considerable number of them and that a certain percentage of patients who developed "pneumonia" may have had community acquired pneumonia that was misclassified as nosocomial if symptoms began before 48 h.

In conclusion, we conducted a large prospective, single center, observational case-control study to identify a combination of PCT, CRP, and WBC that was predictive of postoperative pneumonia or SSI in cardiac surgery patients. By dichotomizing daily postoperative PCT and WBC biomarkers into groups with ≤3 and ≥ 4 elevations, we determined that four elevations over

the first 3 postoperative days was strongly associated with postoperative pneumonia or SSI within the 30 d following cardiac surgery, besides being good predictors of mortality.

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Authors' contributions: M.H.R., J.B.M., and E.T. conceived the idea, designed the protocol, and supervised the analysis of the results. E.G.S., F.J.A., M.L., and E.C. supervised the recruitment of patients and collected the clinical material. I.F., F.J.A., E.C., E.T., and J.B.M. developed and supervised all work and analyzed the results. E.T. wrote the report in collaboration with all the authors.

Disclosure

The authors declare no conflicts of interest.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jss.2017.01.021.

REFERENCES

1. Vincent JL, Sakr Y, Sprung CL, et al. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med*. 2006;34:344.
2. Bates DW, Cook EF, Goldman L, Lee TH. Predicting bacteremia in hospitalized patients. A prospectively validated model. *Ann Intern Med*. 1990;113:495.
3. Bates DW, Sands K, Miller E, et al. Predicting bacteremia in patients with sepsis syndrome. Academic Medical Center Consortium Sepsis Project Working Group. *J Infect Dis*. 1997;176:1538.
4. Sablotzki A, Friedrich I, Mühling J, et al. The systemic inflammatory response syndrome following cardiac surgery: different expression of proinflammatory cytokines and procalcitonin in patients with and without multiorgan dysfunctions. *Perfusion*. 2002;17:103.
5. Garnacho-Montero J, Ortiz-Leyba C, Herrera-Melero I, et al. Mortality and morbidity attributable to inadequate empirical antimicrobial therapy in patients admitted to the ICU with sepsis: a matched cohort study. *J Antimicrob Chemother*. 2008;61:436.
6. Pittet D, Rangel-Frausto S, Li N, et al. Systemic inflammatory response syndrome, sepsis, severe sepsis and septic shock: incidence, morbidities and outcomes in surgical ICU patients. *Intensive Care Med*. 1995;21:302.
7. Wacker C, Prkno A, Brunkhorst FM, Schlattmann P. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. *Lancet Infect Dis*. 2013;13:426.
8. Uzzan B, Cohen R, Nicolas P, et al. Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: a systematic review and meta-analysis. *Crit Care Med*. 2006;34:1996.
9. Jebali MA, Hausfater P, Abbes Z, et al. Assessment of the accuracy of procalcitonin to diagnose postoperative infection after cardiac surgery. *Anesthesiology*. 2007;107:232.
10. Falcoz PE, Laluc F, Toubin MM, et al. Usefulness of procalcitonin in the early detection of infection after thoracic surgery. *Eur J Cardiothorac Surg*. 2005;27:1074.
11. Luzzani A, Polati E, Dorizzi R, et al. Comparison of procalcitonin and C-reactive protein as markers of sepsis. *Crit Care Med*. 2003;31:1737.
12. Luyt CE, Combes A, Reynaud C, et al. Usefulness of procalcitonin for the diagnosis of ventilator-associated pneumonia. *Intensive Care Med*. 2008;34:1434.
13. Delannoy B, Guye ML, Slaiman DH, et al. Effect of cardiopulmonary bypass on activated partial thromboplastin time waveform analysis, serum procalcitonin and C-reactive protein concentrations. *Crit Care*. 2009;13:R180.
14. Fluri F, Morgenthaler NG, Mueller B, et al. Copeptin, procalcitonin and routine inflammatory markers-predictors of infection after stroke. *PLoS One*. 2012;7:e48309.
15. Rothenburger M, Trösch F, Markewitz A, et al. Leukocyte activation and phagocytotic activity in cardiac surgery and infection. *Cardiovasc Surg*. 2002;10:470.
16. Povoa P, Almeida E, Moreira P, et al. C-reactive protein as an indicator of sepsis. *Intens Care Med*. 1998;24:1052.
17. Póvoa P, Coelho L, Almeida E, et al. C-reactive protein as a marker of infection in critically ill patients. *Clin Microbiol Infect*. 2005;11:101.
18. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest*. 1992;101:1644–1655.
19. Pugin J, Auckenthaler R, Mili N, et al. Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. *Am Rev Respir Dis*. 1991;143:1121.
20. Horan TC, Gaynes RP, Martone WJ, et al. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. *Infect Control Hosp Epidemiol*. 1992;13:606.
21. Piccoli M, Cerquetani E, Pastena G, et al. "Lone" increase in C-reactive protein after cardiac surgery: prevalence, clinical characteristics, in-hospital course, and prognostic value. *Eur J Cardiovasc Prev Rehabil*. 2008;15:482.
22. Krumsdorf U, Chorianopoulos E, Pleger ST, et al. C-reactive protein kinetics and its prognostic value after transfemoral aortic valve implantation. *J Invasive Cardiol*. 2012;24:282.
23. Baykut D, Schulte-Herbruggen J, Krian A. The value of procalcitonin as an infection marker in cardiac surgery. *Eur J Med Res*. 2000;5:530.
24. Sponholz C, Sakr Y, Reinhart K, Brunkhorst F. Diagnostic value and prognostic implications of serum procalcitonin after cardiac surgery: a systematic review of the literature. *Crit Care*. 2006;10:R145.
25. Dorge H, Schondube FA, Dorge P, et al. Procalcitonin is a valuable prognostic marker in cardiac surgery but not specific for infection. *Thorac Cardiovasc Surg*. 2003;51 :322.

26. Dallas J, Brown SM, Hock K, et al. Diagnostic utility of plasma procalcitonin for nosocomial pneumonia in the intensive care unit setting. *Respir Care*. 2011; 56:412.
27. Ramirez P, Garcia MA, Ferrer M, et al. Sequential measurements of procalcitonin levels in diagnosing ventilator-associated pneumonia. *Eur Respir J*. 2008;31:356.
28. Luyt CE, Chastre J. Plasma procalcitonin: another arrow in our quiver? *Respir Care*. 2011;56:530.
29. Tamayo E, Álvarez FJ, Martínez-Rafael B, et al. Ventilator-associated pneumonia is an important risk factor for mortality after major cardiac surgery. *J Crit Care*. 2012;27:18.
30. Kamiya H, Tanzeem N, Akhyari P, et al. Impact of severe postoperative complications after cardiac surgery on mortality in patients aged over 80 years. *Ann Thorac Cardiovasc Surg*. 2014;20:383.
31. Al-Nawas B, Krammer I, Shah PM. Procalcitonin in diagnosis of severe infections. *Eur J Med Res*. 1996;1:331.