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Procalcitonin cannot be used as a biomarker of infection in heart surgery patients with acute kidney injury

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ABSTRACT

Purpose: We intended to assess how acute kidney injuy impacts on procalcitonin levels in cardiac surgery patients, with or without infection, and whether procalcitonin might be used as a biomarker of infection in acute kidney injuy.

Material and Methods: A case–control study was designed which included patients that had had cardiac surgery between January 2011 and January 2015. Every patient developing severe sepsis or septic shock (n = 122; 5.5%) was enrolled. In addition, consecutive cardiac surgery patients during 2013 developing systemic inflammatory response syndrome (n = 318) were enrolled. Those recruited 440 patients were divided into 2 groups, according to renal function.

Results: Median procalcitonin levels were significantly higher during the 10 postoperative days in the acute kidney injury patients. Regression analysis showed that postoperatory day, creatinine, white blood cells and infection were significantly ($P < .0001$) associated to serum procalcitonin level. In patients with creatinine ≥2, median procalcitonin levels were similar in infected and non-infected patients. Only when creatinine was less than 2 mg/L, the median procalcitonin levels were significantly higher in patients with infection, as compared to those with no infection.

Conclusions: In acute kidney injuy patients, high procalcitonin levels are a marker of acute kidney injuy but will not be able to differentiate infected from non-infected patients.

1. Introduction

Cardiac surgery is an extended procedure in the developed world, with coronary artery bypass graft (CABG) and valve surgeries being the most common cardiac surgeries performed [1]. In Europe, 348,523 patients underwent cardiac surgery over a 2-year period (2006-2008) [1], with different proportions of CABG and valve surgeries depending on the specific country. In Spain, isolated CABG represents 30% of all cardiac surgeries and isolated valve procedures constitutes 32% [1].

Postoperative sepsis is one of the major complications following cardiac surgery, and an independent predictor of mortality [2,3]. Hospital-acquired infections are common, especially ventilator-associated pneumonia and surgical site infections, with both infections being associated to high morbidity and mortality, and also to longer hospital stay [4,5].

Procalcitonin (PCT) is used as a biomarker of infection [6] and has been successfully used as guidance for the initiation and duration of antibiotic therapy in patients with respiratory infections and to discontinue antibiotic therapy in intensive care unit (ICU) patients, being able to reduce antibiotic use as compared with standard therapy [7,8].

One major limitation of interpreting PCT levels in cardiac surgery patients is that PCT is also one of the inflammatory mediators involved in the inflammatory response elicited by this type of intervention [9,10],

Abbreviations: CABG, coronary artery bypass graft; PCT, procalcitonin; ICU, intensive care unit; CPB, cardiopulmonary bypass; AKI, acute kidney injury; NAKI, no acute kidney injury; CRP, C-reactive protein; WBC, white blood cells.

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leading to a systemic inflammatory response syndrome (SIRS) in most patients [11,12]. Thus, PCT elevations in cardiac surgery patients must be carefully interpreted.

In addition, cardiac surgery patients often develop kidney dysfunction [13], and patients with post-operative, as well as those with preoperative, acute kidney injuy (AKI) show higher rates of infection, which in turn are associated to higher mortality [14]. It would be of most importance, thus, closely monitoring these patients for the presence of infection. The value of PCT assessment in this situation is not clear. Renal dysfunction decreases PCT elimination [15], and while some studies observed no variation or just a small increase of PCT plasma levels in patients with AKI [15,16], a more recent study has shown a marked increase in PCT in 67 patients with postoperative renal dysfunction, either with or without infection [17]. Therefore, we intended to study how AKI impacts on PCT levels in a large series of patients, with or without infection, in the period following cardiac surgery, while assessing other putative variables that might influence in PCT levels, and determine whether PCT levels might still be used to assess infection in cardiac surgery patients presenting with renal dysfunction.

2. Material and methods

2.1. Study population

A case-control study was designed, which included 440 patients that had had cardiac surgery with cardiopulmonary bypass (CPB) at the Hospital Clínico Universitario de Valladolid (Spain) in the period between January 2011 and January 2015. The case group consisted of all patients that 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 = 318). All patients that began receiving antibiotic treatment for suspected infection whose germ culture results were negative were excluded from the study. In a second step, the 440 patients (122 with severe sepsis or septic shock plus 318 with SIRS) were divided in 2 groups according to renal function during the postoperative period: 92 patients were included in the AKI and 348 in the no acute kidney injury (NAKI) arm (Fig. 1).

Blood samples for biologic measurements (PCT, C-reactive protein [CRP], white blood cells [WBC], creatinine, glucose and lactate) were drawn on the first day in the ICU and daily in the morning until the tenth postoperative day. Procalcitonin was measured by an immunoluminometric assay (LUMItest Procalcitonin; Brahms Diagnostica) adapted to the analyzer Cobas 6000 (Roche Diagnostics) with detection limit 0.2 to 100 ng/ml. C-reactive protein was measured by automatic laser nephelometry (BN II analyzer; Siemens Dade Behring); normal values were less than 6 mg/L, and the coefficient of variation of the measurement was less than 5%.

The study was conducted according to the Helsinki Declaration and Good Clinical Practice and was approved by the Institutional Review Board (IRB) of Hospital Clínico Universitario de Valladolid. Waived informed consent was authorized because routine care of the patient was not modified.

2.2. Patients' management in the ICU

The surgical and anesthetic techniques and the treatments received by the patients in the ICU were the ordinary procedures routinely conducted at the hospital. After admission to the ICU and verification of hemodynamic stability, the patients were placed at a 45° position. Gastric protection was routinely carried out with ranitidine (50 mg intravenously per 12 hours) during the first 24 hours of admission in the ICU; if it continued to be required, ranitidine was replaced by sucralfate (1 g orally or through nasogastric tube every 8 hours). All patients were extubated in the ICU when hemodynamically stable. Mouthwashes with chlorhexidine were carried out twice a day. Antibiotic therapy was administered in patients with infection, according to the bacterial pathogens isolated from these patients, as well as following international guidelines.

2.3. Definitions

Diagnosis of infection: clinical assessment of the patient was performed daily in the ICU for infection diagnosis. Severe sepsis and septic

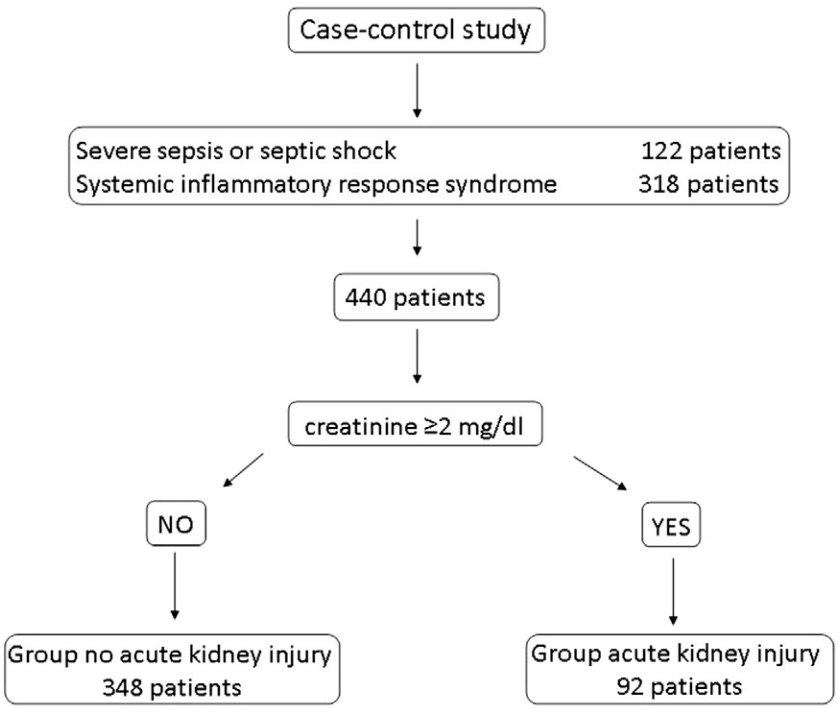

Fig. 1. Study flow diagram.

shock were defined according to the American College of Chest Physicians/Society of Critical Care Medicine consensus classification [18]. The final diagnosis of infection was determined by 2 independent experts, and in cases of disagreement, a consensus was reached by a third expert. The experts diagnosing infection were blinded to the CRP and PCT values.

Diagnosis of AKI: creatinine was measured daily in the ICU. AKI was defined as blood creatinine values 2 mg/dL or greater showing at any time during the first 5 post-operatory days, accompanied by an increase of at least 0.70 mg/dL from preoperative baseline [17].

2.4. Statistical analysis

Categorical variables were described by means of absolute and relative frequencies and continuous variables by central and dispersion measurements. Group comparisons (AKI vs NAKI) were conducted employing the χ^2 test for categorical variables and the independent samples Student *t* test or Mann-Whitney *U* test for continuous variables. In order to assess the putative independent variables [AKI (yes/no), infection (yes/no), post-operative day (1-10 days), WBC counts and CRP, creatinine, lactate and glucose levels] that might influence the dependent variable PCT concentration, correlations were calculated by the non-parametric Spearman rank correlation (ρ). The distributions of continuous variables (concentrations of PCT, PCR, etc) were skewed to the right side, and the values were always transformed to the natural logarithms for the linear regression analysis. Categorical covariates (postoperatory day and infection) were represented by indicator variables. Regression analysis was repeated using only significant variables, and a boosting algorithm was applied in order to improve accuracy. The relative contribution of a specific covariate to the variation in PCT concentrations was expressed by the proportion of the total R2 in the model. Statistical analyses were performed with SPSS 20.0. All P values were two sided, and statistical significance was defined as $P < .05$.

3. Results

Four hundred and forty patients with mean age 67 ± 11 years, 293 (66.6%) men, were included in the analysis. The clinical and sociodemographic characteristics of the AKI and NAKI groups are shown in Table 1. Patients with AKI were significantly older ($P \leq .0001$) but showed similar proportions of comorbidities than patients with NAKI. AKI patients were submitted to more emergency surgeries ($P \leq .0001$) and more mixed-type (valve and CABG) surgeries than AKI patients, and thus, CPB time was also significantly ($P \leq .0001$) longer. Ejection fraction was significantly lower ($P \leq .001$) in patients with acute kidney injuy. As expected, AKI patients had a more severe status (higher APACHEII and SOFA scores) than NAKI patients ($P \leq .0001$), and showed significantly longer length of stay and higher mortality.

Table 1
Sociodemographic and clinical characteristics of the population

Variable	NAKI N = 348	AKI N = 92	*P*
Preoperative factors			
Age (y)	66.4 ± 11.1	71.3 ± 9.6	**≤.0001**
Sex: male	228 (65.5)	65 (70.7)	.353
Hypertension	193 (55.5)	62 (67.4)	.039
Diabetes mellitus	77 (22.1)	19 (20.7)	.761
Obesity	55 (15.8)	15 (16.3)	.907
Alcohol drinking	16 (4.6)	3 (3.3)	.575
Hepatic disease	9 (2.6)	3 (3.3)	.724
Respiratory disease	42 (12.1)	15 (16.3)	.282
CRF	-	19 (20.6)	-
Intraoperative factors			
Emergency surgery	32 (9.2)	30 (32.6)	**≤.0001**
Type of surgery			
Valve	180 (52.0)	40 (44.4)	.2
CABG	108 (31.2)	18 (20.0)	.037
Valve + CABG	58 (16.8)	32 (35.6)	**≤.0001**
Total CPB time (min)	116.6 ± 46.7	153.6 ± 58.2	**≤.0001**
EF (%)	57.0 ± 11.4	50.8 ± 12.2	**≤.0001**
Risk score			
SOFA score (points)	5.7 ± 1.3	7.8 ± 1.9	**≤.0001**
APACHE II score (points)	10.8 ± 3.0	16.4 ± 3.9	**≤.0001**
Postoperative factors			
Poly-transfusion (number)	6 (1.7)	7 (7.6)	**.003**
Length of stay (days)			
Preoperative hospitalization	9.0 ± 9.5	10.2 ± 10.4	.317
Total in hospital	25.1 ± 20.8	43.8 ± 81.4	**.034**
In the ICU after surgery	7.5 ± 14.6	29.4 ± 104.4	**.048**
30-day mortality	11 (3.2)	25 (27.2)	**≤.0001**
Hospital mortality	30 (8.6)	45 (48.9)	**≤.0001**

Values are expressed as n (%) and mean ± SD.
CRF: Chronic Renal Failure; EF: Ejection Fraction; SOFA: Sequential Organ Failure Assessment; SAP II: Simplified Acute Physiology Score II; APACHE II: Acute Physiology and Chronic Health Evaluation II.
In bold: significant *P* values.

3.1. Variables evolution during the first 10 post-operative days

Median WBC counts and median lactate levels followed a similar pattern along the 10 post-operative days in AKI and NAKI patients but with significantly higher counts/levels in the AKI patients (Fig. 2A and B). Median CRP levels also followed a similar pattern in both groups of patients but levels were significantly higher at 3, 4, and 5 postoperative days in the AKI patients (Fig. 2C). Median glucose levels were significantly higher in AKI than NAKI patients at 1, 2, 4, 5, and 8 postoperative days (Fig. 2D). Regarding median PCT levels, they were significantly ($P > .05$) and markedly higher in the AKI than NAKI patients all along the postoperative period, with values in AKI patients being at least about three times those in NAKI patients (Fig. 3A). Median PCT levels were 6- and 8-fold above those in NAKI patients, at days two and three respectively. Median PCT values were also more stable in NAKI patients, ranging from 0.12 ng/mL on day 1 to 0.94 ng/mL on day 4, while in AKI patients values started at 0.37 ng/mL on day 1 and peaked at 4.04 ng/mL on day 3. Median serum creatinine levels, as expected, were significantly higher in NAKI than RF patients, being also more stable in these later ones (Fig. 3B). From post-operative day 2 onwards, the median creatinine level in AKI patients was above 2 mg/L, peaking at day 3.

3.2. PCT levels in infected and no infected patients

Patients were grouped in those who had an infection during the post-operative period and those who did not. In patients with infection, PCT median levels were significantly larger in AKI than NAKI patients all along the first 10 post-operative days with a peak at day 3 in RF patients (Fig. 4A). The AKI and NAKI curves resemble those of the overall transplanted population. In patients with no infection, median PCT levels were also significantly higher than those in NAKI patients during the first 4 post-operative days with a peak at the third post-operative day (Fig. 4B).

3.3. Correlation analysis

The putative independent variables [infection (yes/no), postoperative day (1-10 days), WBC counts and CRP, creatinine, lactate, and glucose levels] were assessed for correlation with the dependent variable PCT concentration, by the non-parametric Spearman rank correlation (ρ) test. PCT values were correlated with WBC count ($\rho = 0.24$, $P < .0001$), CRP ($\rho = 0.39$, $P < .0001$), creatinine ($\rho = 0.49$, $P < .0001$), post-operatory day ($\rho = 0.30$, $P < .0001$) and infection ($\rho = 0.33$, $P < .0001$). However, PCT did not correlate with serum lactate ($\rho = -0.03$, $p > 0.05$) or glucose ($\rho = 0.01$, $P > .05$). Those variables found to be correlated were tested to find out their relative contribution to the PCT value by step-forward multiple regression analysis. The variables still significantly associated to PCT are shown in Table 2.

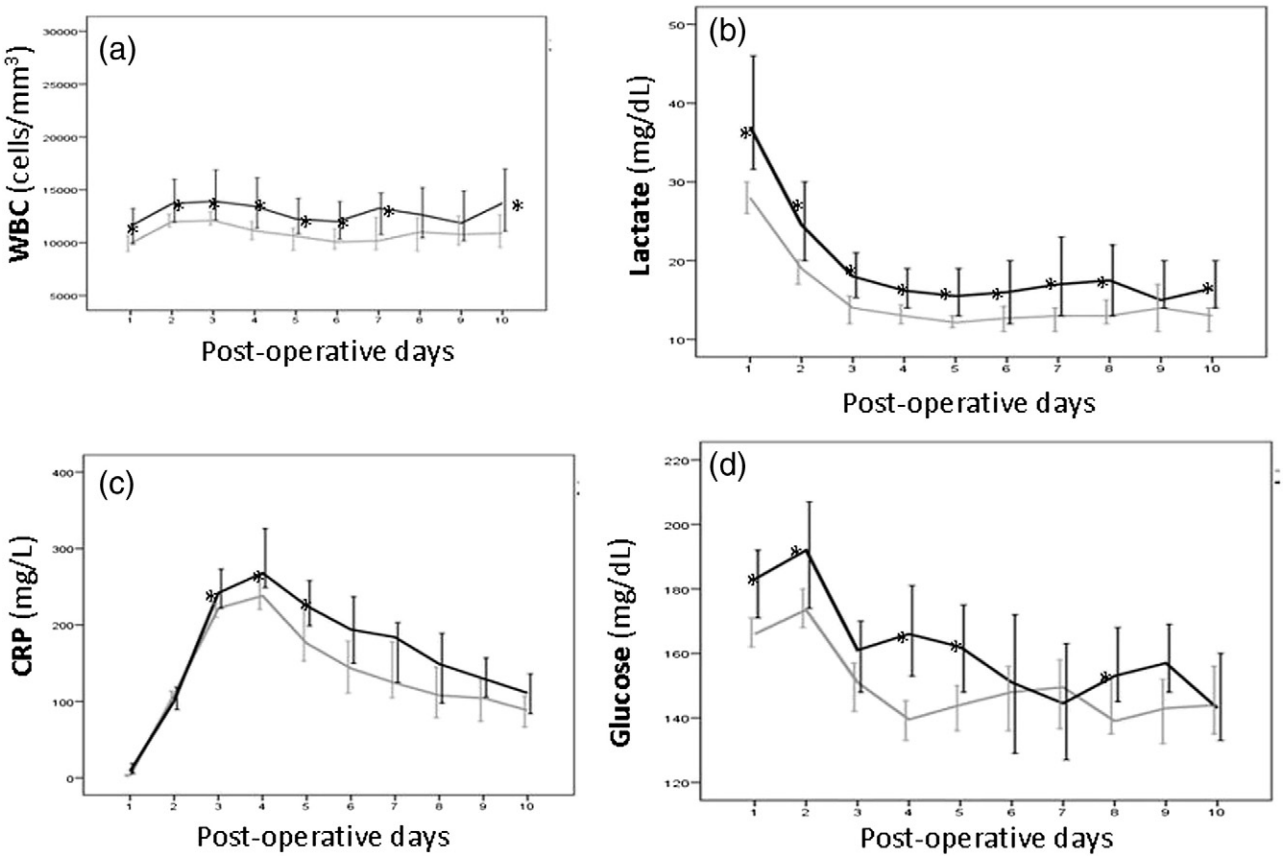

Fig. 2. Median (95% CI) WBC counts (A), and lactate (B), CRP (C) and glucose levels (D) (95% CI) in AKI (darker line) and NAKI (lighter line) patients during the first 10 post-operative days. $P \leq .05$.

3.4. PCT levels

Median PCT values accumulated during the 10 postoperative days, and according to level of renal function and the presence or not of infection are shown in Table 3. PCT levels were significantly higher in AKI than NAKI patients ($P < .0001$) and in patients with infection vs. no infection ($P < .0001$). However, when patients had AKI, high PCT levels were a marker of AKI, as compared to patients with NAKI, but were not able to differentiate infected from non-infected patients.

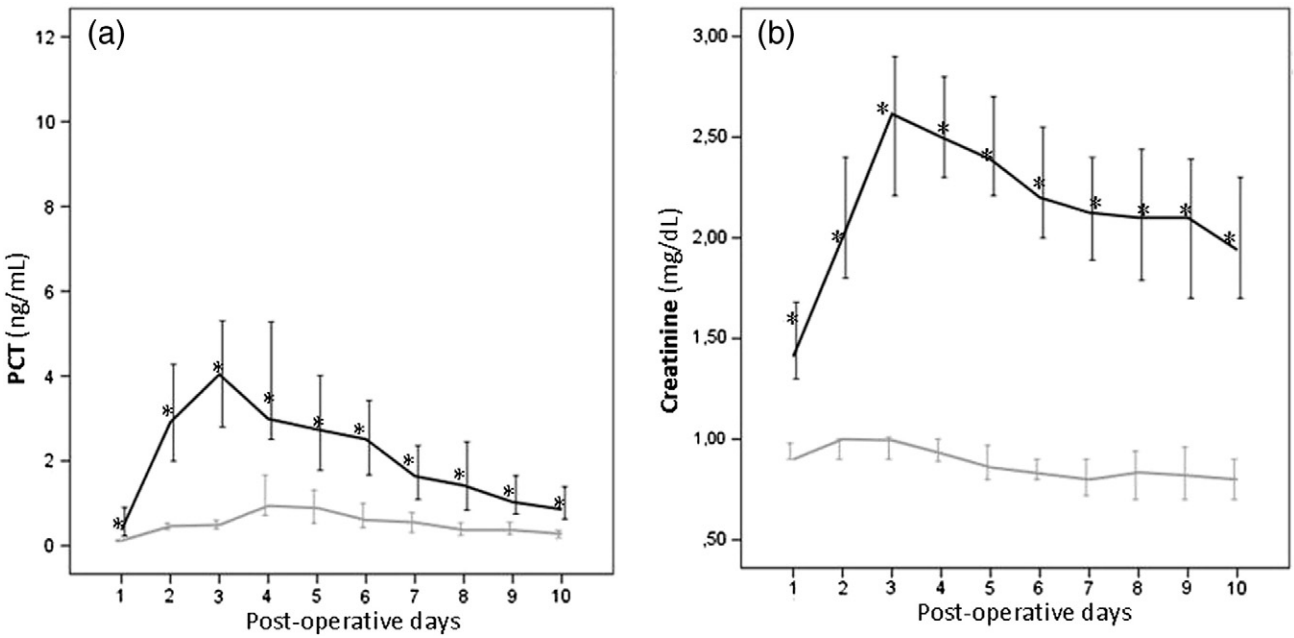

Fig. 3. Median (95% CI) PCT levels (A) and creatinine levels (B) in patients AKI (darker line) and NAKI (lighter line) during the first 10 post-operative days. *$P \leq .05$.

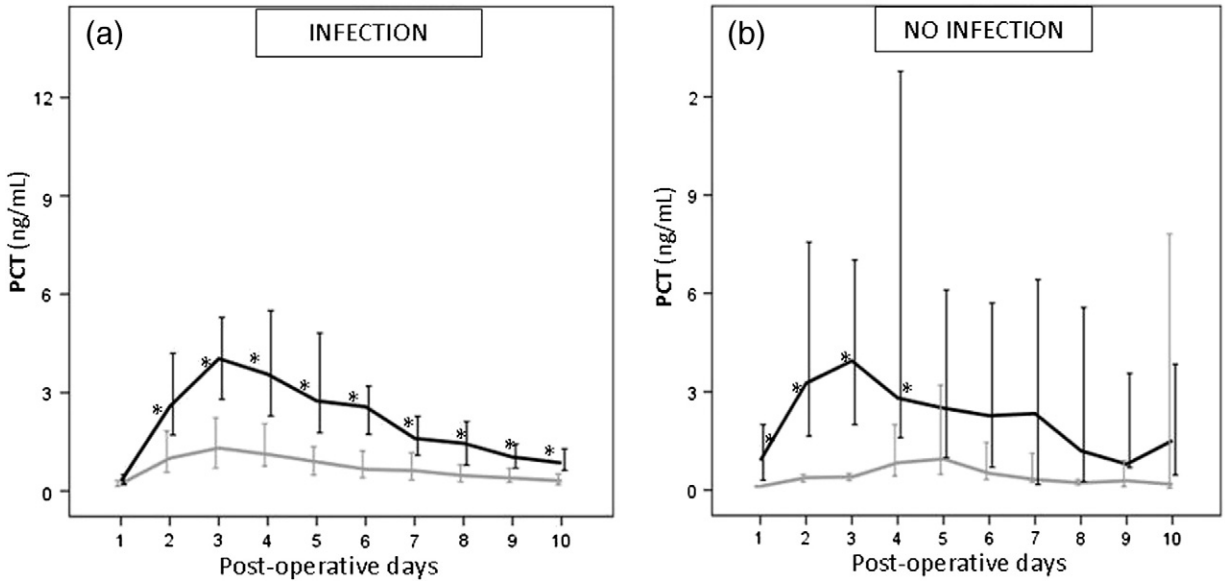

Fig. 4. Median (95% CI) PCT levels in patients with infection (A) and with no infection (B), presenting with AKI (darker line) or NAKI (lighter) during the first 10 post-operative days ($P \leq .05$).

Fig. 5 shows PCT levels in patients with and without infection at different levels of serum creatinine. As long as the creatinine level increases, so does the PCT, both in infected and non-infected patients. PCT values between 1 and 2.5 ng/mL are frequent in patients with elevated creatinine (≥2 mg/dL), even if there is no infection. PCT values above 2.5 ng/mL are probably due to infection if creatinine is <2 mg/dL but when creatinine is >2 mg/dL, those high PCT values are frequent in both, infected and non-infected patients. Overall, when patients have creatinine ≥2 mg/dL, the differences in PCT levels between patients with and without infection are not significant. However, when creatinine is less than 2 mg/dL, the median PCT levels are significantly higher in patients with infection, as compared to those with no infection.

4. Discussion

The present study showed a positive association between PCT concentration in serum in heart surgery patients and creatinine concentration, WBC count, the presence of infection and the post-operatory day also contributing to the PCT level. Elevated creatinine levels (≥2 mg/L), as those presented in acute kidney injuy, compromise the diagnostic value of PCT as an infection biomarker.

Table 2
Multiple linear regression of total serum PCT (ng/mL) in natural logarithm on clinical covariates, and their relative contributions to the variation of total serum PCT concentrations

Variable		B (SD)	*P*	Relative contribution	with BOOSTING
Constant		−3.383 (0.601)	0.000		
Postoperatory day (*)	1	−0.646 (0.167)	0.000		
	2	0.730 (0.168)	0.000		
	3	0.939 (0.171)	0.000		
	4	1.030 (0.186)	0.000		
	5	0.882 (0.193)	0.000	27.0%	37%
	6	0.667 (0.194)	0.001		
	7	0.613 (0.199)	0.002		
	8	0.296 (0.200)	0.138		
	9	0.229 (0.206)	0.266		
Creatinine		1.084 (0.061)	0.000	27.0%	43.5%
WBC		0.252 (0.062)	0.000	23.0%	6%
Infection: YES (**)		0.422 (0.077)	0.000	23.0%	13.5%

$R^2 = 0.372$ after boosting.
(*) Reference: 10th postoperatory day.
(**) Reference: Infection NO.

The median PCT value accumulated during the 10 postoperative days was significantly higher in infected than uninfected patients, in agreement with previous studies showing PCT as a marker of infection in critically ill patients [6]. When focusing on renal function, median PCT values in AKI patients were at least almost three times those in NAKI patients (Fig. 3). This marked increase in PCT levels in AKI, as compared to NAKI patients, was observed in infected, as well as non-infected patients, at least during the first four post-operative days (Fig. 3), which agree with previous studies [17].

In the Amour study [17], median PCT levels in AKI patients with no infection peaked on day 2 at about 0.8 ng/mL, while in patients with infection peaked at about 2 ng/mL. However, in our study, AKI patients, whether infected or not, had similar median PCT values peaking on post-operative day 3 at about 4 ng/mL (Fig. 3). Therefore, it seems that PCT cannot be used as a biomarker of infection in patients with AKI. Previous studies had shown that in chronic kidney disease patients, as estimated glomerular filtration rate (GFR) declined, PCT increased, causing confusion if these patients were to be evaluated for infection [19]. Other studies, however, showed that PCT could be used in identifying patients with systemic infections among patients with renal dysfunction by using raised cutoff values [20].

PCT is partly eliminated in the urine and the amount eliminated was reduced in patients with impaired renal function [15]. However, the disappearance rate of PCT and creatinine clearance were only weakly correlated. In our study, however, a marked increase in plasma PCT levels

Table 3
Median PCT values accumulated during the 10 postoperative days, and according to level of renal function and the presence or not of infection

PCT levels with accumulated data (10 days)			
	Median	IQR	*P*
NAKI	0.39	0.13-1.09	.0001
AKI	2.03	0.80-5.51	
Infection	1.13	0.39-3.70	.0001
No infection	0.37	0.10-1.26	
NAKI			
No Infection	0.30	0.09-0.86	.0001
Infection	0.55	0.26-1.54	
AKI			
No Infection	2.00	0.57-7.43	.887
Infection	2.05	0.82-5.20	

IQR: interquartile range.
In bold: Significant *P* values.

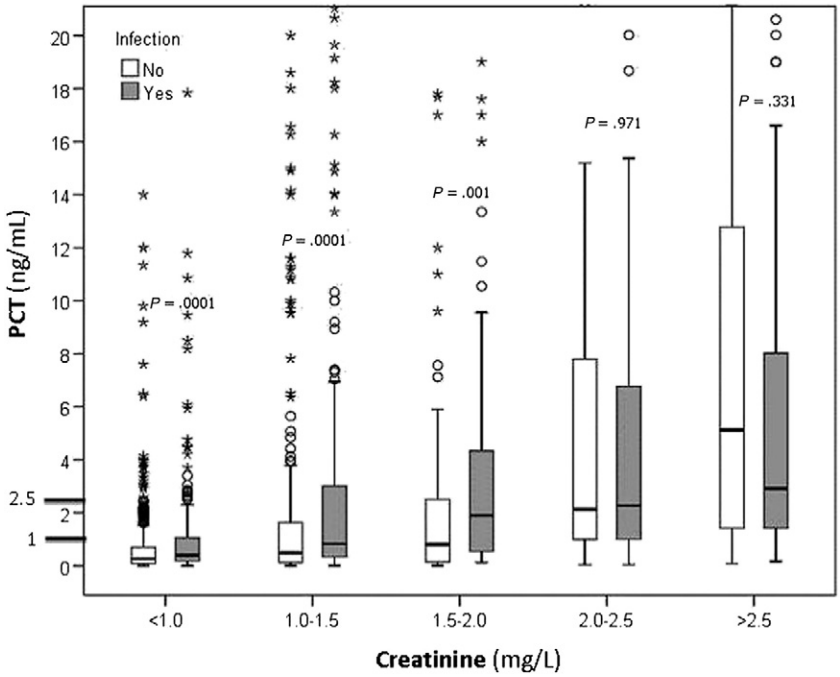

Fig. 5. Procalcitonine levels in patients with and without infection at different levels of serum creatinine (AKI: creatinine ≥2). Data are depicted as box plot diagrams (logarithmic scale). The box represents the range of values from the 10% percentile (lower bar) to the 90% percentile (upper bar). The horizontal line within the box represents the median and the vertical line signifies the maximum and minimum values.

was observed in patients with acute kidney injuy. It is important to point out that PCT has direct cytotoxic properties on mesangial cells and thus, an increase in PCT might further affect the kidney function and indirectly further increase the plasma PCT level [21].

As expected, AKI patients were significantly older, since older age is a known factor for postoperative acute acute kidney injuy [22,23]. Fifty percent of AKI patients presented with acute kidney injuy before surgery. In fact, increased preoperative serum creatinine is the most important predictive risk factor for post-operative AKI [13,23]. Regarding postoperative factors, WBCs and C-reactive proteins are inflammatory mediators, and have been shown to be associated to post-operative infection [24,25]. Acute kidney injuy is associated to inflammatory stages [26], and thus, median WBC counts and C-reactive protein levels were significantly higher in patients with acute kidney injuy (CRP only in postoperative days 3–5), as compared to those with no AKI. Median lactate levels were also significantly higher in AKI than NAKI patients, since the lactate concentration is also associated to renal dysfunction [27]. It is well known that hyperglycemia produces structural alterations at the renal level inducing renal damage [28]. On multivariate analysis, a higher level of glucose (>150 mg/dl) and glycaemic variability were identified as independent risk factors for postoperative acute kidney failure in cardiac surgery patients [29]. In agreement with these data, glucose levels were, at several post-operative days, significantly higher in AKI than NAKI patients, and levels showed greater variations in AKI patients.

The study shows some limitations. First, we assessed renal function using serum creatinine, which is an unreliable biomarker since it lags behind the decline in GFR by days, and it is also affected by factors such as age, race, and muscle mass [13]. Although an estimation of the GFR from prediction equations that take into account the mentioned factors would have been more accurate, the estimation of serum creatinine is easy and fast and has been previously used to estimate acute kidney injuy in the post-operative period [30]. Second, the study was conducted in a single center. However, the current study was conducted in a large number of patients (440); it is one of the few studies assessing PCT in cardiac surgery patients in conjunction with AKI; and it was conducted in the routine clinical practice, which reflects the evolution of the parameters in real world clinical circumstances.

5. Conclusions

In conclusion, PCT levels in the postoperative period after cardiac surgery are influenced by creatinine, WBCs, presence of infection and postoperatory day. The creatinine level is the factor influencing PCT the most, and thus, in case of AKI, PCT levels will not be able to be used as a marker of infection. Elevated creatinine levels (≥2 mg/dL), as those presented in acute kidney injuy, compromise the diagnostic value of PCT as an infection biomarker. Thus, although procalcitonin-guided antibiotic treatment in heart surgery patients, encouraged when PCT ≥0.5 ng/mL, has been shown to be safe and to reduce the cost of postoperative care, it should not be used when creatinine is ≥2 mg/dL.

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Conflicts of Interest: None

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