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Predictive value of the kinetics of procalcitonin and C-reactive protein for early clinical stability in patients with bloodstream infections due to Gram-negative bacteria

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ABSTRACT

Objective: To investigate whether the magnitude of the change in procalcitonin (PCT) and C-reactive protein (CRP) levels between day 1 and day 2 after the blood culture date is associated with early clinical stability (ECS) on day 3 in patients with bacteremia due to Gram-negative bacteria (GNB).
Materials/methods: A prospective cohort study carried out in a 950-bed tertiary hospital in Spain between March 2013 and May 2014. Patients with GNB bacteremia were included. Changes in PCT and CRP kinetics from day 1 to day 2 (Δ%PCT, Δ%CRP) were expressed as percentage of decline in blood levels. Logistic regression was used to identify predictors of ECS. Classification and regression tree analysis was performed to identify breakpoints. The discriminatory power of Δ%CRP and Δ%PCT as predictors of ECS was assessed by the area under the ROC (AUROC).
Results: 71 patients were included, and 53 (74.56%) reached ECS. Multivariate analyses showed that SOFA score on day 1, Δ%PCT, and Δ%CRP were associated with ECS after controlling for confounders. Δ%PCT ≥ 30% (decline) and Δ%CRP ≥ 10% (decline) predicted ECS only among patients with SOFA≤3 on day 1 ($n = 54$; 43 reached ECS). In these patients, the AUROCs for the prediction of ECS were 0.96 (95% CI: 0.90–1) for Δ%CRP and 0.96 (95% CI: 0.90–1) for Δ%PCT, respectively.
Conclusions: In the subgroup of patients with a SOFA score on day 1 ≤3, a ≥30% decline in PCT or a ≥10% decline in CRP between day 1 and day 2 was a very good predictor of ECS (which in turn was associated with a lower 30-day mortality and a greater clinical cure on day 14). Patients who do not achieve this decrease may need more intensive workup. In this subgroup (with a SOFA on day 1 ≤3), CRP may be preferred due to its lower cost.

1. Introduction

Bloodstream infections (BSIs) are a leading cause of morbidity and mortality. Appropriate management during the early stages of BSI is critical in order to improve outcomes. Indeed, in patients with BSI, early active antimicrobial therapy is associated with lower mortality (Retamar et al. 2012). On the other hand, excessive use of broad-spectrum agents is a major driving force behind increased antimicrobial resistance (Dellit et al. 2007). Despite the fact that most positive blood cultures are detected in less than 15 h (Martínez et al. 2007), full susceptibility test results typically take another 2–3 days, so decisions about narrow-spectrum or broad-spectrum antimicrobial coverage in the first 48–72 h or the need for further evaluation are challenging in patients with BSI, particularly when the clinical data are not specific enough to suggest a clear improvement or deterioration. The availability of biomarkers to help guide clinical judgment in these decisions may therefore be useful.

Procalcitonin (PCT) is currently being investigated as a biomarker for systemic bacterial infections and sepsis (Wacker et al. 2013). It is synthesized in numerous extrathyroid tissues as a response to lipopolysaccharides and bacterially induced cytokines (Linscheid et al. 2004; Müller et al. 2000). Within approximately 3 to 6 h of the clinical manifestation of sepsis, plasma levels of PCT increase but fall rapidly if the sepsis is controlled. C-reactive protein (CRP) is an acute-phase protein synthesized by the liver in response to cytokine stimulation, and

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serum levels increase markedly within hours of onset of infection, inflammation, or tissue injury. In patients with systemic infections, changes in CRP levels typically occur later than PCT. CRP is a marker for inflammation, traditionally used as a complementary tool to support clinical diagnosis and a marker of severity of disease (Lobo 2012).

The kinetics of PCT and CRP for monitoring patients with sepsis and respiratory infections have already been evaluated (Bouadma et al. 2010; Coelho et al. 2012; Hochreiter et al. 2009; Karlsson et al. 2010; McCluskey et al. 2017; Schuetz et al. 2012) and been shown to have implications for prognosis, with falling values correlating with good results, and static or increasing values with adverse outcomes, mainly mortality (Hoeboer and Groeneveld 2013; Jung et al. 2013; Ríos-Toro et al. 2017). Nevertheless, the relative value of marker changes for predicting response to antibiotic treatment in bloodstream infections has barely been studied. Apart from this, analyzing kinetics associated with variables with short-term outcomes, such as early clinical stability, would enable us to state with greater assurance that the possible associations observed were not due to other variables or to unknown circumstances intervening between the study variable and the outcome variable. The aim of this study therefore was to test the hypothesis that the magnitude of relative changes in PCT and CRP concentrations between day 1 and day 2 after blood cultures are performed is associated with early clinical stability after controlling for clinical assessment data.

2. Material and methods

2.1. Setting and design

This prospective cohort study was performed in a 950-bed tertiary hospital in Seville, Spain, from March 2013 through May 2014. Admitted patients with monomicrobial bacteremia due to Gram-negative bacteria were eligible and were included if they fulfilled all of the following criteria: a) aged ≥18 years; b) sepsis criteria on the day the blood cultures were taken (day 0) (Levy et al. 2001); c) empirical treatment was administered within 6 h after blood cultures were taken; d) at least one criterion for clinical instability was present on day 1 (see below); and e) the patient was alive on day 2. All patients included in the study were followed for 30 days. The STROBE recommendations for reporting results of observational studies (Von Elm et al. 2008) were followed. The local Review Board approved the study. The need to obtain informed consent was waived due to the observational nature of the study.

Patients were detected using the daily reports of positive blood cultures from our Microbiology Department. As part of the bacteremia program in our center, clinical microbiologists actively report the Gram stain results of all positive blood cultures, and infectious diseases specialists provide active consultation and follow-up for all patients with BSI from that moment. Blood samples for basic biochemistry, blood count, CRP and PCT levels were tested on days 1 and 2.

2.2. Variables and definitions

Data collected included age; gender; bacterial species; nosocomial, community or healthcare-associated acquisition of infection; type and severity of underlying conditions, using the Charlson comorbidity index (Charlson et al. 1987); type of hospital service; source of BSI determined from clinical and microbiological data, following CDC criteria (Horan et al. 2008); severity of sepsis on day 0 (Levy et al. 2001); severity of acute illness according to Pitt score (Hilf et al. 1989), assessed daily; sequential organ failure assessment (SOFA) score (Vicent et al. 1996), assessed daily; antimicrobial therapy; source control (defined as debridement, drainage, or removal of device when applicable); mortality until day 30; and length of stay. The main outcome variable was early clinical stability (ECS) measured on day 3 (see definition below). The secondary outcome variable was clinical cure on day 14.

Antimicrobial therapy administered before susceptibility results were available was considered empirical; therapy administered afterwards was considered definitive. Nosocomial acquisition was considered when symptoms of infection began 48 h or more after hospital admission or less than 48 h after hospital discharge. Otherwise, the case was considered to be community-onset. If community-onset, the episode was considered healthcare-associated if any of the following criteria applied in the previous 3 months: hospitalization in an acute care center; any kind of dialysis, surgery, specialized home, or outpatient care; any kind of invasive procedure (endoscopy, urinary, or vascular catheterization); residence in a long-term care facility.

Clinical stability was defined as the absence of all the following (unless accounted for by another well-characterized disease unrelated to BSI): a) body temperature >38 °C or <35 °C; b) hypotension (systolic blood pressure <90 mmHg, median arterial pressure <70 mmHg, or a systolic blood pressure decrease >40 mmHg from basal values); c) heart rate >90 beats/min; d) arterial hypoxemia (ratio of arterial oxygen tension [PaO2]/fraction of inspired oxygen [FiO2] <300; in patients not admitted to intensive care units, oxygen saturation <95% was used as an indicator of potential hypoxemia and investigated accordingly); (e) leukocytosis (WBC count >12,000 μL^{-1}) or leukopenia (WBC count <4000 μL^{-1}); f) creatinine increase >0.5 mg/dL from basal levels; g) thrombocytopenia (platelet count <100,000 μL^{-1}); h) hyperbilirubinemia (plasma total bilirubin >4 mg/dL); and i) altered mental status, according to baseline situation (Hilf et al. 1989). A physician not involved in the study and blinded to CRP and PCT values evaluated whether the patients had reached clinical stability or not.

PCT kinetics was expressed as the percentage difference in PCT concentrations on day 2 compared to day 1 using the following formula: $\Delta\% PCT_{day1\text{-}day2} = (PCT_{day2} - PCT_{day1}) / PCT_{day1} * 100$. Values <0 indicated decreasing PCT concentrations. CRP kinetics was expressed in the same way.

2.3. Laboratory methods

Blood for serum samples was collected by venipuncture, and samples were processed in <60 min. Serum PCT and CRP levels were measured with the Cobas 6000 system (Hitachi High-Technologies Corporation, Tokyo, Japan) using the Elecsys Brahms PCT Assay (B·R·A·H·M·S AG, Hennigsdorf, Germany) and Roche Diagnostics (Mannheim, Germany), respectively. CRP was quantified by immunoturbidimetric assay, with functional sensitivity of 1 mg/L. PCT was quantified by ECLIA (electrochemiluminescence) assay, with functional sensitivity of 0.02 ng/mL. The Biochemistry Clinical Laboratory in our hospital is registered in the External Quality Control Program of the Spanish Society of Biochemistry.

Blood cultures were processed using the automated BD BACTEC™ FX system (Becton-Dickinson Microbiology Systems). Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) recommendations for performing, processing, and interpreting blood cultures were followed (Loza Fernández de Bobadilla et al.). Identification and antimicrobial susceptibility testing were performed using the Wider system (Soria-Melguizo, Madrid, Spain). Susceptibility results were interpreted according to Clinical Laboratory Standards Institute (CLSI) recommendations (Clinical and Laboratory Standard Institute 2010).

2.4. Statistical analyses

Data are presented as absolute numbers and percentages, or medians and interquartile range (IQR, 25th–75th percentile). Patients who reached and did not reach ECS were compared. Continuous variables were compared using the Student's *t* test or the Mann–Whitney *U* test, as appropriate. Categorical variables were compared using the χ^2 test.

The discriminatory power of $\Delta\%CRP_{day1\text{-}day2}$ and $\Delta\%PCT_{day1\text{-}day2}$ as predictors of ECS was assessed by calculating the area under the receiver operating characteristic curve (AUROC), with 95% confidence intervals (CIs). The optimal threshold on the curve was considered to be the sum of maximum sensitivity plus specificity. Additionally, classification and regression tree (CART) analysis was performed to identify predictors of ECS and their optimal cutoff points.

To control for confounders, multivariate analyses using logistic regression were performed, with ECS and clinical cure on day 14 as dependent variables and $\Delta\%CRP_{day1\text{-}day2}$ or $\Delta\%PCT_{day1\text{-}day2}$ as the explanatory variables of interest (PCT and CRP models were constructed separately). Potential confounders and interactions were entered into the models if the univariate *P* value was <0.1 and selected manually using backward elimination. Change in PCT and CRP levels was retained in the models. The Akaike information criterion (Akaike 1974) was used to select the final models for PCT and CRP. The models chosen were those that minimized Kullback–Leibler divergence between the model and the actual data. We calculated the variance inflation factor value for every variable included in the multivariate models to control for potential collinearity.

The analyses were performed using R software (version 3.0.1). CART software 8.0 (Salford Systems) was used for CART analysis.

3. Results

Overall, 71 patients were included: 53 patients reached ECS (74.6%) and 18 did not. The characteristics of patients according to ECS on day 3 are shown in Table 1. The most frequent *Enterobacteriaceae* were *Escherichia coli* and *Klebsiella pneumoniae*, and the most frequent sources of BSI were the urinary tract or the biliary tract. There were statistically significant differences in both groups for Charlson score, Pitt index on days 1 and day 2, SOFA score on days 1 and 2, as well as $\Delta\%PCT_{day1\text{-}day2}$ and $\Delta\%PCR_{day1\text{-}day2}$. Absolute PCT levels on days 1 and 2 were lower among patients who reached ECS, although the differences were only significant on day 2. CRP concentrations were significantly lower among patients with ECS on day 2. In addition, there were also differences in cure on day 14 and 30-day mortality.

We calculated the basic ROC curve generated by quantitative variables significantly associated with ECS (Table 2). All variables showed good predictive ability, except for Charlson score and $\Delta SOFA_{day1\text{-}day2}$. The highest AUROC values (>0.80) were for Pitt score on day 1 (0.83), Pitt score on day 2 (0.87), SOFA score on day 1 (0.85), SOFA score on day 2 (0.86), $\Delta\%CRP_{day1\text{-}day2}$ (0.81), and $\Delta\%PCT_{day1\text{-}day2}$ (0.84). For $\Delta\%PCT_{day1\text{-}day2}$, the optimal threshold corresponded to a decrease of 33.3% (specificity, 0.82; sensitivity, 0.89). For $\Delta\%CRP_{day1\text{-}day2}$, the optimal threshold was a 12.0% decrease (specificity, 0.65; sensitivity, 0.87).

Additionally, separate CART analyses were performed to evaluate the predictive capacity of $\Delta\%PCT_{day1\text{-}day2}$ and $\Delta\%\ PCR_{24\text{-}48h}$ for reaching ECS, including other covariates (age, gender, source of infection, Charlson, SIRS severity, Pitt score, SOFA score, etiology, acquisition, and appropriate empirical therapy). CART analysis selected the variable $\Delta\%PCT_{day1\text{-}day2}$ (Fig. 1A) as predictive of ECS in patients with SOFA ≤3 on day 1 (all 43 patients with $\Delta\%PCT_{day1\text{-}day2} \leq -30\%$ reached ECS, but only 6/11 [54.5%] of those with lower decreases), although the same variable ($\Delta\%PCT_{day1\text{-}day2}$) was not selected as a predictor for patients with SOFA>3. Similarly, CART analysis also selected $\Delta\%PCR_{day1\text{-}day2}$ (Fig. 1B) as predictive of ECS in patients with SOFA ≤3 (all 44 patients with $\Delta\%\ CRP_{24\text{-}48h} \leq -10\%$ achieved ECS, but only 5/10 [50%] of those with lower decreases). $\Delta\%\ PCR_{day1\text{-}day2}$ was not selected as predictive of ECS for the patient group with SOFA >3.

Multivariate analyses confirmed that SOFA value on day 1, $\Delta\%\ PCT_{day1\text{-}day2} \leq -30\%$, and $\Delta\%\ PCR_{day1\text{-}day2} \leq -10\%$ were significantly associated with both ECS and cure on day 14 (except for $\Delta\%\ PCR_{day1\text{-}day2} \leq -10\%$,Table 3).

To confirm these results, four AUROCs were calculated for $\Delta\%\ PCT_{day1\text{-}day2}$ and $\Delta\%\ PCR_{day1\text{-}day2}$ in each subgroup with SOFA scores of ≤3 and >3 on day 1. In the SOFA ≤3 subgroup (Fig. 2A), both variables were highly predictive of ECS (0.96 [95% CI: 0.90–1] and 0.96 [95% CI: 0.90–1], respectively; p = 0.91, DeLong test), whereas in the subgroup with SOFA >3 (Fig. 2B), their predictive ability was lower, although

Table 1
Features of included patients according to whether or not they reached early clinical stability (on day 3).[a]

	Patients not reaching ECS (*n* = 18)	Patients reaching ECS (*n* = 53)	*P*
Demographics			
Age, median (IQR)	65.5 (60–70.5)	68 (58–77)	0.56[b]
Male	8 (44.4)	20 (37.7)	0.61
Systemic inflammatory response syndrome			
Severe sepsis or septic shock	13 (72.2)	27 (50.9)	0.12
Source of infection			0.20
Urinary or biliary tract	13 (72.2)	44 (83.0)	
Intraabdominal infection	3 (16.7)	2 (3.8)	
Vascular catheter	0	3 (5.7)	
Other	2 (11.1)	4 (7.5)	
Underlying patient conditions			
Charlson, median (IQR)	3.5 (1–5.75)	2 (0–2)	0.04[c]
Pitt day 1, median (IQR)	2 (1–3)	0 (0–1)	<0.001[c]
Pitt day 2, median (IQR)	2 (1–3)	0 (0–0)	<0.001[c]
$\Delta Pitt_{day1\text{-}day2}$, median (IQR)	0 (0–0)	−0.75 (−1 to 0)	0.002[c]
SOFA on day1, median (IQR)	4.5 (2.5–7.5)	1 (0–2)	<0.001[c]
SOFA on day2, median (IQR)	4.5 (3.25–7.75)	0 (0–2)	<0.001[c]
$\Delta SOFA_{day1\text{-}day2}$, median (IQR)	0 (0–0.07)	0 (−0.5 to 0)	0.01[c]
Acquisition			
Nosocomial infection	6 (33.3)	11 (20.8)	0.28
Etiology			0.10
Escherichia coli	12 (66.7)	39 (73.6)	
Klebsiella pneumoniae	5 (27.8)	4 (7.5)	
Enterobacter spp.	0	4 (7.5)	
Others	1 (5.6)	6 (11.3)	
PCT concentration (ng/mL)			
Day 1, median (IQR)	19.7 (7.2–37.9)	8.0 (4.0–40.2)	0.19[c]
Day 2, median (IQR)	18.1 (8.7–56.7)	5.15 (2–13.0)	0.002[c]
$\Delta\%PCT_{day1\text{-}day2}$, median (IQR)	−8 (−24.0 to 92.6)	−46.2 (−56.5 to −37)	<0.001[c]
CRP concentration (mg/L)			
Day 1, median (IQR)	329 (226.8–451.8)	205.0 (133.0–330.0)	0.06[c]
Day 2, median (IQR)	329.5 (230.7–445.3)	160.4 (97.0–241.0)	<0.001[c]
$\Delta\%CRP_{day1\text{-}day2}$, median (IQR)	1.7 (−21.3 to 30.6)	−32.0 (−44.0 to −21.0)	<0.001[c]
Therapy			
Appropriate empirical therapy	16 (88.9)	48 (90.6)	0.84
Source control performed	8 (44.4)	18 (34)	0.42[c]
Outcomes			
30-day mortality	5 (27.8)	1 (1.9)	0.003[d]
Clinical cure on day 14	6 (33.3)	50 (94.3)	<0.001

[a] Except where otherwise specified, data represent no. (%) of patients. *P* values were calculated by χ^2 test, except where otherwise specified. PCT = procalcitonin; CRP = C-reactive protein; IQR = interquartile range.
[b] Student's *t* test.
[c] Mann–Whitney *U* test.
[d] Fisher's exact test.

Table 2
Univariate estimates of AUROCs for predicting ECS.

Variable	AUROC	95% CI	Optimal threshold	Specificity	Sensitivity
Charlson	0.66	0.50–0.83	3	0.50	0.91
Pitt on day 1	0.83	0.71–0.94	0	0.82	0.77
Pitt on day 2	0.87	0.76–0.97	0	0.82	0.83
$\Delta Pitt_{day1\text{-}day2}$	0.72	0.59–0.86	−0.67	0.82	0.55
SOFA on day 1	0.85	0.72–0.97	3	0.72	0.92
SOFA on day 2	0.86	0.74–0.98	2	0.77	0.92
$\Delta SOFA_{day1\text{-}day2}$	0.68	0.56–0.80	−0.10	0.30	1
PCT on day 2	0.75	0.61–0.89	6.9	0.88	0.60
$\Delta PCT_{day1\text{-}day2}$	0.84	0.70–0.98	−33%	0.82	0.89
CRP on day 2	0.78	0.62–0.93	280	0.64	0.90
$\Delta CRP_{day1\text{-}day2}$	0.81	0.70–0.93	−12%	0.65	0.87

better for PCT than for PCR kinetics (0.86 [95% CI: 0.68–1] and 0.68 [95% CI: 0.42–0.93] respectively, p = 0.09; DeLong test).

4. Discussion

For most patients with positive blood cultures, the Gram stain results (and now, identification of the causative bacteria using MALDI-TOF) are generally available during the first 24 h, although final susceptibility data usually take another 1–2 days. Consequently, clinical decisions about changes in antimicrobial therapy and source control during this time window are based solely on clinical grounds. Our experience is that, when dealing with patients with bacteremia, uncertainties about the need to change empirical therapy or to carry out a more aggressive search for the source of BSI when it is not obvious frequently arise in the first 2 days. Predictive biomarkers for reaching ECS could be very useful in this situation. Our data showed that several variables such as SOFA, Pitt score, and the kinetics of CRP and PCT between day 1 and day 2 are good individual predictors of ECS. This discriminative capacity for ECS was even better when SOFA on day 1 (at the time when BSI due to Gram-negative bacteria is confirmed) was considered simultaneously with the kinetics of CRP or PCT. In our analysis, in the subgroup of patients with SOFA scores ≤3, the kinetics of CRP and PCT were both very good predictors of ECS.

The prognostic value of CRP and PCT kinetics has been studied in several types of infection, with mortality as the main outcome variable. Several studies have associated CRP and/or PCT kinetics in the first days after onset of pneumonia (Zhydkov et al. 2015), ventilator-associated pneumonia (Seligman et al. 2006), bacteremia (Póvoa et al. 2005), sepsis (Póvoa et al. 2011; Schuetz et al. 2013), or septic shock (Jung et al. 2013) with mortality. Other studies have assessed whether CRP and PCT kinetics in the first days were associated with use of appropriate (active) empirical therapy (Charles et al. 2009; Odermatt et al. 2017; Schuetz et al. 2017). However, the predictive value of the kinetics of these biomarkers for reaching clinical stability has scarcely been studied. Yan Shi reported a significant association in patients with nosocomial pneumonia between PCT decline in the first 3 days of infection and clinical stability assessed within 5 days of end of treatment or the third week of antimicrobial treatment (Shi et al. 2014). SOFA score in combination with PCT and/or CRP levels has been used to predict sepsis in critical patients (Matsumura et al. 2014) and to decide whether to discharge patients admitted to the ICU (Yang et al. 2016). To the best of our knowledge, however, no other published study has evaluated the combination of SOFA score and the kinetics of PCT or CRP to assess outcomes such as ECS in patients with monomicrobial Gram-negative BSI.

One advantage of analyzing the association of the kinetics of PCT and CRP with ECS is the narrow time interval between the 2 events being compared. This contrasts with other studies in which there was a long time interval between the predictor and outcome variable, during which the influence of other variables or unforeseen circumstances may have been very important, yet was frequently not taken into consideration. Here, the evolution of PTC and CPR at the time analyzed

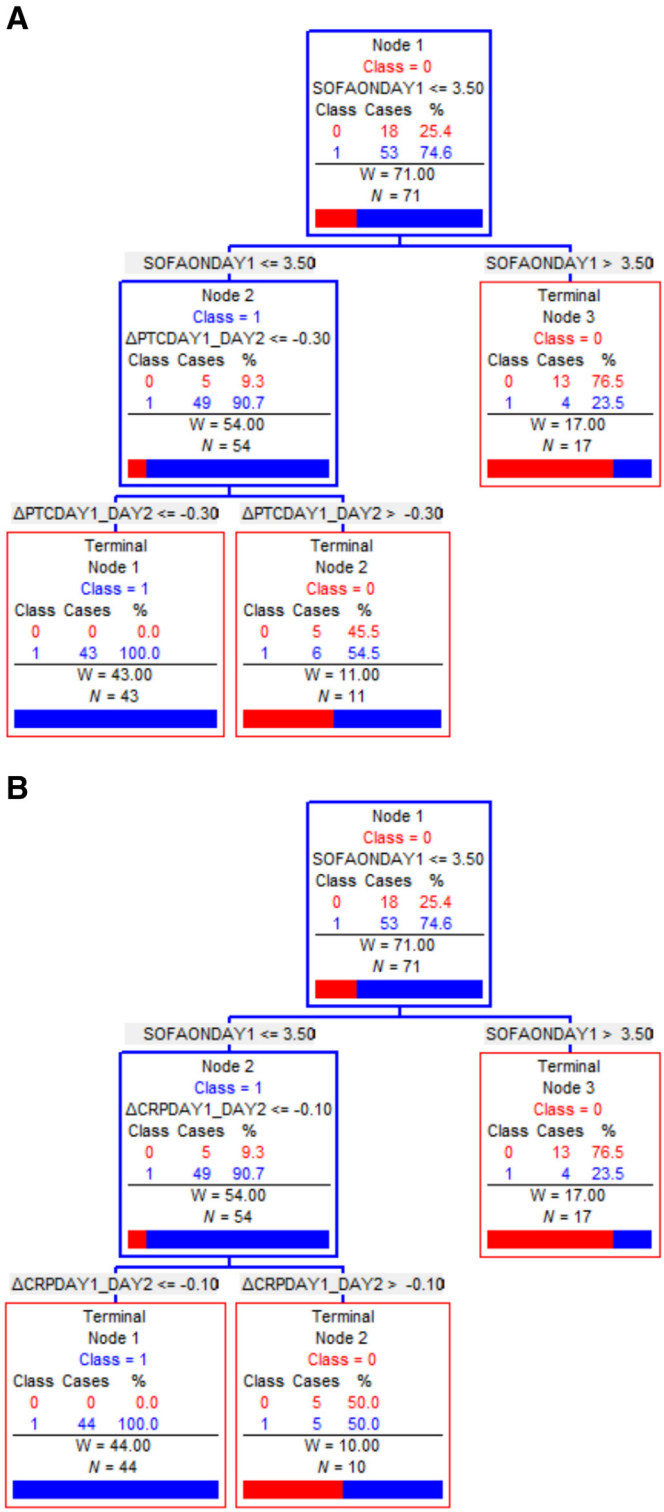

Fig. 1. CART model obtained to identify ECS predictors (A) Considering $\Delta PCT_{day1\text{-}day2}$ in the model (1 = reached ECS; 0 = did not reach ECS). (B) Considering $\Delta CRP_{day1\text{-}day2}$ in the model (1 = reached ECS; 0 = did not reach ECS).

was directly related to the clinical situation of the patient 24 h later, as is shown by the high predictive capacity indicated by the very high AUROCs generated in our study in the subgroup of patients with SOFA score ≤3. Furthermore, as has been stated in other studies (Castelli et al. 2004; Ferreira et al. 2001; Sakr et al. 2012), ECS was related to clinical cure on day 14 and 30-day patient survival in our study. Since delay in administering appropriate treatment is associated with an increased

Table 3
Univariate and adjusted odds ratios of variables included in different models associating the kinetics of PCT or CRP with prediction of ECS or cure on day 14.

	ECS				Cure on day 14			
	Univariate		Adjusted		Univariate		Adjusted	
Models considering ΔPCT[a]	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
$\Delta PCT_{day1\text{-}day2}$ <−30%	36.5 (9.1–198)	<0.001	73.9 (11.5–1034.9)	0.001	7.36 (2.1–28.4)	0.002	4.57 (1.05–21.0)	0.04
SOFA on day 1	0.43 (0.26–0.63)	<0.001	0.29 (0.12–0.69)	0.005	0.56 (0.39–0.75)	<0.001	0.62 (0.43–0.83)	0.004
Models considering ΔCRP[b]	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
$\Delta CRP_{day1\text{-}day2}$ <−10%	12.0 (3.5–46.3)	<0.001	10.3 (1.90–55.6)	0.007	6.13 (1.77–22.7)	0.005	3.11 (0.66–14.3)	0.13
SOFA on day 1	0.43 (0.26–0.63)	<0.001	0.44 (0.27–0.72)	0.001	0.56 (0.39–0.75)	<0.001	0.61 (0.42–0.80)	0.002

[a] All variance inflation factor values of the variables included in the final multivariate models were less than 1.2.
[b] All variance inflation factor values of the variables included in the final multivariate models were less than 1.1.

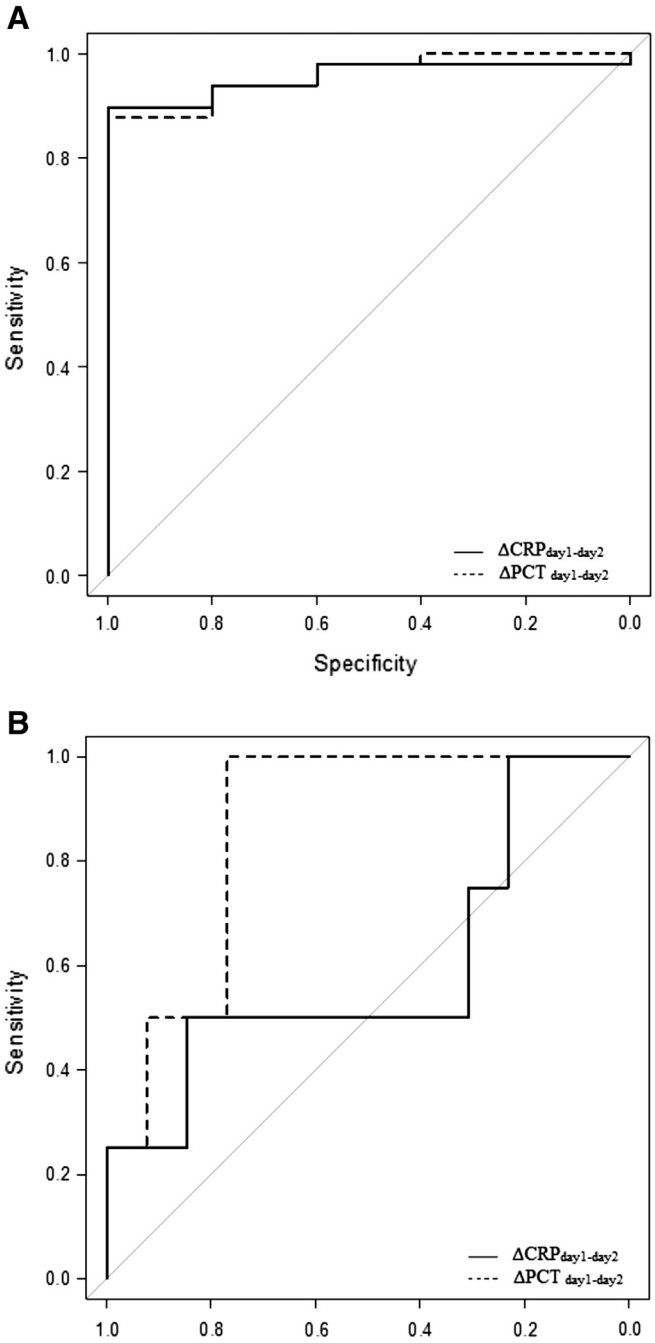

Fig. 2. AUROC of $\Delta CRP_{day1\text{-}day2}$ and $\Delta PCT_{day1\text{-}day2}$ for prediction of ECS according to SOFA on day 1. (A) In the subcohort of patients with SOFA on day 1 ≤3 (DeLong test p = 0.91) (B) In the subcohort of patients with SOFA >3 (DeLong test p = 0.09).

risk of mortality in bacteremia (Retamar et al. 2012), this association could be helpful for clinicians in the management of sepsis by adding information about response to empirical therapy before the antibiogram results, influencing the decision of whether to maintain or change therapy in accordance with whether PTC and CPR were expected to decrease or not. In any event, decreased PTC and CPR values in the period studied were also associated with clinical cure on day 14.

Some limitations of this study should be mentioned. First, the small sample size and the very strict criteria used prevented us from conducting survival analysis (mortality on day 30) with CRP and PCT kinetics in the first 72 h after blood cultures (only 6 deaths in the 71 cases included). A study with a larger sample size would better determine the effect of CRP and PCT decreases and their ability to predict ECS, mainly in the subgroup of patients with SOFA score >3 on day 1. Second, there may have been unmeasured confounders. Finally, since most of the cases included in the study had a urinary or biliary tract source, our results apply only to monomicrobial Gram-negative BSIs with the same sources. The proportion of decrease in concentrations on day 1 and day 2 was greater for PCT than for CRP, according to another study that suggested a slower kinetics of CRP (Odermatt et al. 2017).

Regarding which of the two biomarkers, PCT or CRP, is the most suitable for appropriate management of early-stage sepsis, our study did not obtain significant results that enabled us to opt for one rather than the other in the subgroup of patients with SOFA ≤3. However, given the higher cost of obtaining PCT concentrations, compared to CRP, and balancing that against their similar predictive capacities, it seems appropriate to choose CRP as the biomarker decision tool for this subgroup of patients. In contrast, for the subgroup of patients with SOFA >3 on day 1, we were unable to confirm the usefulness of kinetics of either of the 2 markers on day 1 and day 2 in connection with the clinical management of these patients. In any case, the small sample size in this subgroup reduced the statistical power of the analysis.

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Conflicts of interest

JRB has received honoraria from Merck for accredited educational activities and from AstraZeneca for coordinating a research project. AP has received honoraria from Merck for accredited educational activities. PR has received honoraria from Merck for accredited educational activities and from Roche for scientific advisory. The authors declare no conflicts of interest for this study. All other authors declare no conflicts of interest.

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