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C-reactive protein and albumin kinetics after antibiotic therapy in community-acquired bloodstream infection

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ABSTRACT

Objectives: We assessed C-reactive protein (CRP) and plasma albumin (PA) kinetics to evaluate community-acquired bloodstream infection (CA-BSI) patients' 1-year outcomes.
Methods: Population-based study, with CRP and PA measurements on day 1 (D1) and D4. Relative CRP variations in relation to D1 CRP value were evaluated (CRP-ratio). Patients were classified as fast response, slow response, non-response, and biphasic response.
Results: A total of 935 patients were included. At D4, the CRP-ratio was lower in survivors on D365 in comparison with D4–D30 non-survivors and D30–D365 non-survivors ($p < 0.001$). In comparison with fast response patients, non-response and biphasic response patients had 2.74 and 5.29 increased risk, respectively, of death in D4–D30 and 2.77 and 3.16 increased risk, respectively, of death in D31–D365. PA levels remained roughly unchanged from D1–D4, but lower D1 PA predicted higher short and long-term mortality ($p < 0.001$). The discriminative performance of the CRP-ratio and D1 PA to identify patients with poor short and long-term mortality after adjustments was acceptable (AUROC = 0.79).
Conclusions: Serial CRP measurements at D1 and D4 after CA-BSI is clinically useful to identify patients with poor outcome. Individual patterns of CRP-ratio response with PA at D1 further refine our ability of predicting short or long-term mortality.

Introduction

Community-acquired bloodstream infection (CA-BSI) is a well-defined infectious clinical entity that is associated with high morbidity and mortality, particularly in patients with previous comorbidities (Gradel et al., 2013). In addition, CA-BSI outcome depends markedly on the timing and adequacy of empiric antibiotic therapy (Póvoa et al., 2005b; Kumar, 2014).

The diagnosis of CA-BSI is based on a combination of clinical, laboratory and microbiology criteria (Gross et al., 1994). Currently, the assessment of patient response to antibiotic therapy relies on the resolution of the same criteria as used for diagnosis, e.g. fever and leukocytosis, which are very unspecific and also poorly sensitive (Halm et al., 1998; Kaukonen et al., 2018). To overcome these limitations, clinicians frequently use biomarker kinetics, in particular C-reactive protein (CRP) and procalcitonin (Póvoa et al., 2011, 2016).

For 47 ventilator-associated pneumonia patients and 44 CA-BSI patients, we found that the patterns of CRP-ratio response to antibiotic therapy were markedly associated with mortality and clinical course, as early as day 4 (Póvoa et al., 2005a, 2005b). But its impact on long-term outcomes has never been evaluated.

We have previously shown that plasma albumin (PA) decreases significantly just before the CA-BSI diagnosis (Gradel et al., 2018b).

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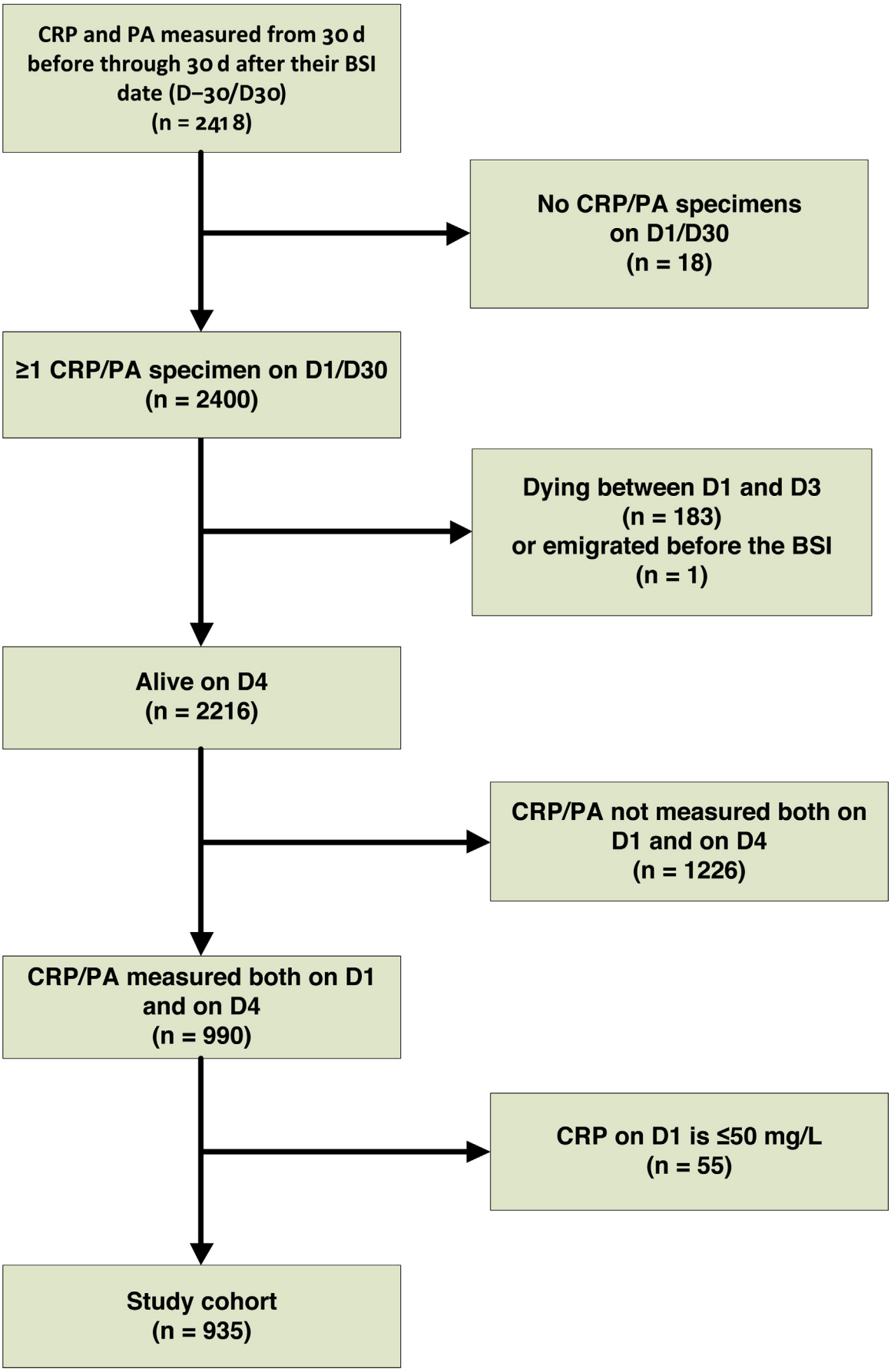

Figure 1. Derivation of the study cohort.

As far as we are aware, the value of PA kinetics has never been studied in the assessment of CA-BSI response to antibiotic therapy.

The Danish Observational Registry of Infectious Syndromes (DORIS) is a population-based research database comprising a high number of CA-BSI patients as well as their data before and after the reference CA-BSI episode, namely biochemistry and microbiologic data (Gradel et al., 2013, 2018b).

This gave us the opportunity to assess CRP and PA kinetics in response to antibiotic therapy in order to identify patients' outcomes, and to validate the concept of patterns of CRP-ratio response to antibiotics.

Materials and methods

Setting

The Danish national health system, covering both primary and hospital care, is tax financed and consequently free of charge for the individual patient. All residents have a unique civil registration number used for all health contacts and linkage between health administrative registries (Schmidt et al., 2014). The admission of all residents with acute illnesses from a well-defined geographical region to a hospital prompted a population-based study based on data from registries (vital status, diagnoses, laboratory data) and the medical records (sepsis severity and CNS dysfunction on admission) in the DORIS research database (Gradel et al., 2013, 2018b). Sepsis was categorized as severe sepsis/septic shock if organ dysfunction or hypotension (systolic blood pressure <90 mmHg) occurred. Because data on hypoperfusion were not valid we did not distinguish between severe sepsis and septic shock (Gradel et al., 2013).

Study cohort

The DORIS research database has been described in detail elsewhere (Gradel et al., 2013). In brief, it comprised all adults (>14 y) residing in Funen County with a first episode of CA-BSI, in the period 2000–2008, a total of $N = 2785$ patients. For the present study, the cohort comprised the 2418 patients with ≥1 measurement of CRP and PA on the same day within a time period from 30 days before through 30 days after the CA-BSI date (Gradel et al., 2018b). A CA-BSI was defined as BSI occurring <3 days after hospital admission and without inpatient contact in the preceding 7 days. We had all the CA-BSI patients' CRP and PA measurements from 2000 through 2010 (Gradel et al., 2018b). Patients with unrealistically low levels of PA (<11 g/L) at the day of the CA-BSI diagnosis were excluded ($N = 3$, 0.12%). The CRP values below the limit of detection (<10 mg/L in 2000–2003, $N = 324$ [2.0%]; <5 mg/L in 2004–2009, $N = 259$ [1.6%]) were randomly allocated a value in the range 0–9 mg/L (for CRP <10 mg/L) or 0–4 mg/L (for CRP <5 mg/L), as described elsewhere (Gradel et al., 2018b).

We refer to Figure 1 for derivation of the study cohort. To capture the most relevant measurement, we initially retrieved the highest CRP and the lowest PA value within the first 24 h of the CA-BSI diagnosis date (designated D1). The cohort of the present study comprised 935 patients alive on D4 with CRP/PA measured on D1 and on D4, their CRP on D1 was >50 mg/L (Chan et al., 2004; Gaini et al., 2006; Knudtzen et al., 2014), and their vital status could be assessed as from D1.

Analyses of CRP and PA levels

All analyses were performed by the Department of Clinical Biochemistry and Pharmacology, Odense University Hospital (OUH) and results were recorded in the Netlab (Medasys S.A., Littau, Switzerland) database. Both CRP and PA were measured on Modular P® (Roche, Mannheim, Germany), CRP using an immune-turbidimetric principle and PA by use of a bromocresol green dye-binding method. All specimen dates refer to date of draw of blood specimens.

Definitions

Due to the biological properties of CRP (Vigushin et al., 1993; Póvoa, 2002), we assessed the relative CRP variations (CRP-ratio). The CRP-ratio was calculated on D4 in relation to the CRP value on D1.

Patients were classified according to an individual pattern, previously defined (Póvoa et al., 2005a), of a CRP-ratio response to antibiotic therapy: fast response – when the CRP-ratio at D4 was <0.4 of the D1 CRP; slow response – characterized by a continuous, but slow, decrease of the CRP-ratio, which was ≥0.4 and <0.8 on D4; non-response – when the CRP-ratio always remained ≥0.8 of the D1 value; biphasic response – characterized by an initial CRP-ratio decrease to levels <0.8 of the D1 CRP, followed by a secondary rise to values ≥0.8.

For PA, no individual patterns after an infection have to our knowledge been reported in the literature. Because the one-time level of PA on D1 was a strong prognostic mortality predictor in our study cohort (Magnussen et al., 2016) we incorporated this in the model.

Statistical analysis

Initially, we computed contingency tables with categorical and continuous variables of baseline characteristics.

We determined two outcomes, D4–D30 (short term) and D31–D365 (long term) mortality.

Box plots of CRP and PA were computed on D1, D2, D3, and D4 in relation to whether patients died on D4–D30, died on D31–D365, or were alive on D365 (excluding patients censored before D365 as their results were insignificantly different from patients alive on D365). We performed a nonparametric test for trend across ordered groups (Cuzick, 1985) for the three patients groups in relation to their mean CRP and PA levels on each of the days D1, D2, D3, and D4. We reiterated the box plots by computing ratios on D2, D3, and D4 in comparison to D1 and performed linear regression analyses to deduce whether the ratios differed from D1.

We further computed Kaplan–Meier curves covering D4–D365, of the four CRP-ratio response patterns and PA quartiles on D1 and used the log-rank test to assess whether the curves differed.

The differences between hazard ratios in Cox proportional hazards regression analyses and odds ratios (ORs) in logistic regression analyses were insignificant as there was almost complete follow-up (data not shown). Hence, we applied the latter, with D4–D30 and D31–D365 mortality as outcomes, as this enabled the subsequent computation of receiver operating characteristic (ROC) curves and the area under these (AUROC). Initially, we performed three models, one with the four CRP-ratio response patterns, one with PA on D1, and one in which the CRP-ratio response patterns were combined with PA on D1. We reiterated these models by the amendment of gender, age, the Charlson comorbidity index (0, 1–2, >2 points) (Charlson et al., 1987), the main bacterial groups (mono-microbial Gram-positive, mono-microbial Gram-negative, poly-microbial), and number of organ dysfunctions (0, 1, >1). For all models, we reported ORs and AUROCs with 95% confidence intervals (CIs) and we evaluated whether AUROCs differed significantly from each other (DeLong et al., 1988).

All two-sided p-values <0.05 were considered significant.

The Stata software (v.14.2, StataCorp, TX, USA) was used for all analyses.

Results

Baseline characteristics

The baseline clinical characteristics at the day of CA-BSI diagnosis are presented in Table 1. At CA-BSI diagnosis, 18.8% presented with sepsis, 58.7% with severe sepsis or septic shock, and 65.0% with one or more organ dysfunctions. A number of 147 (15.7%) and 197 (21.1%) patients died on D4–D30 and D31–D365, respectively, whereas 60 (6.4%) patients with their CA-BSI between 31 May 2008 and 31 December 2008 were censored before D365 as they were alive on the latest vital status date (31 May 2009).

Kinetics of CRP levels

Regardless of patient group (alive on D365, dead D4–D30, dead D31–D365), CRP levels decreased from D1 to D4 and they were significantly lower on D3 and D4 in comparison to D1 (all $p \leq 0.01$) (Figure 2, upper panel). There were no differences between the three patients' groups on D1 ($p = 0.23$) or D2 ($p = 0.39$). On D3 and D4, the CRP levels differed significantly; survivors on D365 presented the lowest CRP levels followed by D31–D365 non-survivors, with the highest levels in D4–D30 non-survivors ($p \leq 0.01$). Patients censored before D365, all of whom were alive at least 154 days after their CA-BSI, did not differ from patients alive on D365 (data not shown).

Table 1
Baseline patient characteristics ($n = 935$).

Text	Number (%)[a]
Age, years	
Mean, SD	66.7, 15.9
Females	429 (45.9)
Charlson comorbidity index	
0 points	194 (20.8)
1–2 points	396 (42.4)
>2 points	345 (36.9)
Sepsis severity	
No sepsis	35 (3.7)
Possibly sepsis	116 (12.4)
Sepsis	176 (18.8)
Severe sepsis or septic shock	549 (58.7)
Organ dysfunction without sepsis	59 (6.3)
Number of organ dysfunctions	
0	327 (34.9)
1	337 (36.0)
≥2	271 (29.0)
Microbiological isolates	
Mono-microbial Gram-positive	365 (39.0)
Staphylococcus aureus	150 (16.0)
Streptococcus pneumoniae	126 (13.5)
Streptococci, other	66 (7.1)
Enterococcus faecalis	23 (2.5)
Mono-microbial Gram-negative	474 (50.7)
Escherichia coli	327 (35.0)
Klebsiella spp.	37 (4.0)
Pseudomonas aeruginosa	34 (3.6)
Other	76 (8.1)
Poly-microbial	96 (10.3)
Vital status data	
Dead day 4–30	147 (15.7)
Dead day 31–365	197 (21.1)
Alive on day 365	531 (56.8)
Censored before day 365[b]	60 (6.4)
Admitted to, on day of CA-BSI	
Surgery	97 (10.4)
Medical	651 (69.6)
Intensive care unit	58 (6.2)
Oncology/hematology	123 (13.2)
Unknown	6 (0.6)

[a] Except for "age, years", cf. text.
[b] All alive on day 154.SD, standard deviation; CA-BSI, community-acquired bloodstream infection.

Kinetics of PA levels

PA levels did not differ on D2, D3, or D4 in comparison to D1 (all $p \leq 0.29$) (Figure 2, lower panel). They rose slightly on D4, except for patients dying on D4–D30, which was unchanged in comparison to D3 levels. On all days, there were clear trends of decreasing PA levels over the three patient groups ($p < 10^{-4}$). Patients censored before D365 did not differ from patients alive on D365 (data not shown).

Mortality characteristics in relation to CRP-ratio response patterns and PA quartiles on D1

Among the 342 patients with a fast CRP-ratio pattern, 222 (64.9%) were alive on D365 (Table 2). The percentage of patients alive on D365 declined over slow response, non-response, and biphasic response patterns (55.3%, 41.5%, and 39.7%, respectively). There was no clear trend for death in D31–D365 or for patients censored before D365, whereas a clear increasing trend was seen for death in D4–D30, from 10.2% in the fast CRP-ratio pattern to 33.3% in the biphasic CRP-ratio pattern.

For PA quartiles on D1, an increasing percentage was alive on D365 as the quartile increased (from 42.7% in the lowest to 70.1% in the highest quartile, Table 2). It was especially deaths on D4–D30 that contributed to this, especially in the two lower quartiles where 20.4% and 28.6% died, in contrast to the two higher quartiles (PA ≥30 g/L) where no more than 10.6% died.

Kaplan–Meier mortality curves

The increasing mortality from fast response, over slow response, non-response, and biphasic response, as depicted in Table 2, was confirmed in the Kaplan–Meier mortality curves (Figure 3, upper panel). Likewise, the higher mortality parallel to lower PA quartile on D1 was seen (Figure 3, lower panel).

Logistic regression analyses

For both D4–D30 and D31–D365 mortality, ORs (95% CIs) in the unadjusted and adjusted models did not differ materially (Table 3). Likewise, the ORs of the patterns of CRP-ratio responses or PA on D1 changed little when both of these were included in the models. The CRP-ratio response pattern showed a clear trend of increasing ORs from fast to biphasic response for both mortality outcomes. For PA on D1 with D4–D30 mortality as the outcome, the OR was 0.90, whereas it was 0.94 (adjusted) or 0.95 (unadjusted) with D31–D365 mortality as the outcome.

AUROCs for the logistic regression models

Regardless of outcome, the CRP-ratio response patterns contributed relatively little to the AUROC (0.61 for D4–D30 and 0.57 for D31–D365 mortality) (Table 4). PA on D1 rendered an AUROC of 0.70 for the D4–D30 mortality, whereas its AUROC of 0.59 contributed less to the prediction of D31–D365 mortality. The combination of the CRP-ratio response pattern and PA on D1 increased the AUROCs 0.04 in comparison to the models with only PA on D1. The amendment of covariates in the full model (age, gender, comorbidity, bacteria, number of organ dysfunctions) increased the AUROCs by 0.05–0.15, with the highest AUROC of 0.79 for the complete model with the D4–D30 mortality as outcome.

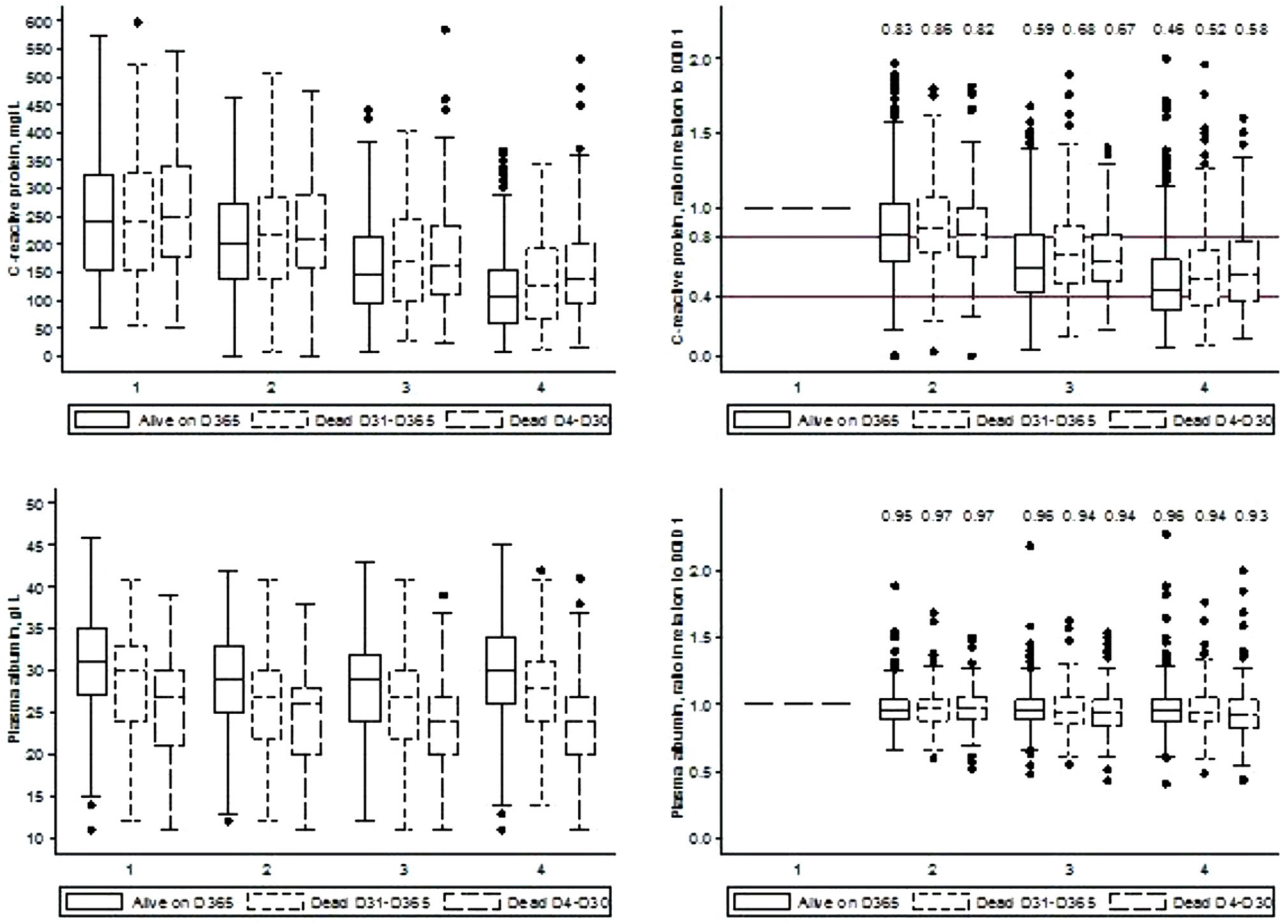

Figure 2. Box plots of C-reactive protein (CRP) and plasma albumin (PA) on day 1, 2, 3, and 4, for patients alive on day 365, dead in day 31–365, and dead in day 4–30. Absolute levels in the left column and ratios in relation to day 1 in the right column. For ratios, median levels are shown in the top. For CRP ratios, a horizontal line is depicted for 0.4 and 0.8.

Table 2
Mortality in relation to C-reactive protein (CRP) ratio response pattern and plasma albumin quartile on day 1.

Text	Total	Alive on day 365	Censored before day 365	Dead day 31–365	Dead day 4–30
CRP-ratio response pattern					
Fast response	342	222 (64.9)	24 (7.0)	61 (17.8)	35 (10.2)
Slow response	465	257 (55.3)	27 (5.8)	104 (22.4)	77 (16.6)
Non-response	65	27 (41.5)	7 (10.8)	17 (26.2)	14 (21.5)
Biphasic response	63	25 (39.7)	2 (3.2)	15 (23.8)	21 (33.3)
Plasma albumin quartile on D1					
11–24 g/L	206	88 (42.7)	8 (3.9)	51 (24.8)	59 (28.6)
25–29 g/L	216	112 (51.9)	15 (6.9)	45 (20.8)	44 (20.4)
30–33 g/L	235	136 (57.9)	17 (7.2)	57 (24.3)	25 (10.6)
34–46 g/L	278	195 (70.1)	20 (7.2)	44 (15.8)	19 (6.8)
Total	935	531 (56.8)	60 (6.4)	197 (21.1)	147 (15.7)

Discussion

In the present study we evaluated the short and long-term mortality in a large cohort of CA-BSI patients, as assessed by serial measurements of CRP and PA. In patients alive on D4 we found that the absolute and relative changes of CRP were markedly higher in survivors and the identification of the individual CRP-ratio pattern of response was independently associated both with D4–D30 and D31–D365 mortality. In addition, we found that lower PA on D1 independently predicted higher D4–D30 and D31–D365 mortality.

There are several studies that assess the clinical response by evaluating the course of CRP after prescription of antibiotics (Póvoa et al., 2005a, 2005b; Coelho et al., 2007; Bruns et al., 2008; Lisboa et al., 2008; Moreno et al., 2010; Póvoa et al., 2011, 2017). Altogether, survivors present a D3/D4 CRP around 60% of the initial value, whereas it remains roughly unchanged in non-survivors. However, concerning BSI the evaluation of CRP kinetics has only been done previously in a pilot study with a small sample size ($N = 44$) (Póvoa et al., 2005b).

In our study, with a much larger cohort of BSI ($N = 935$), all community-acquired, CRP (absolute and relative changes) presented the same course. Among patients alive on D4, those with good short and long-term mortality was just below 46% of the D1 level whereas it was 58% for those dying up to D30 (AUROC = 0.61).

We subsequently classified our patients according to the individual patterns of CRP-ratio response as published elsewhere

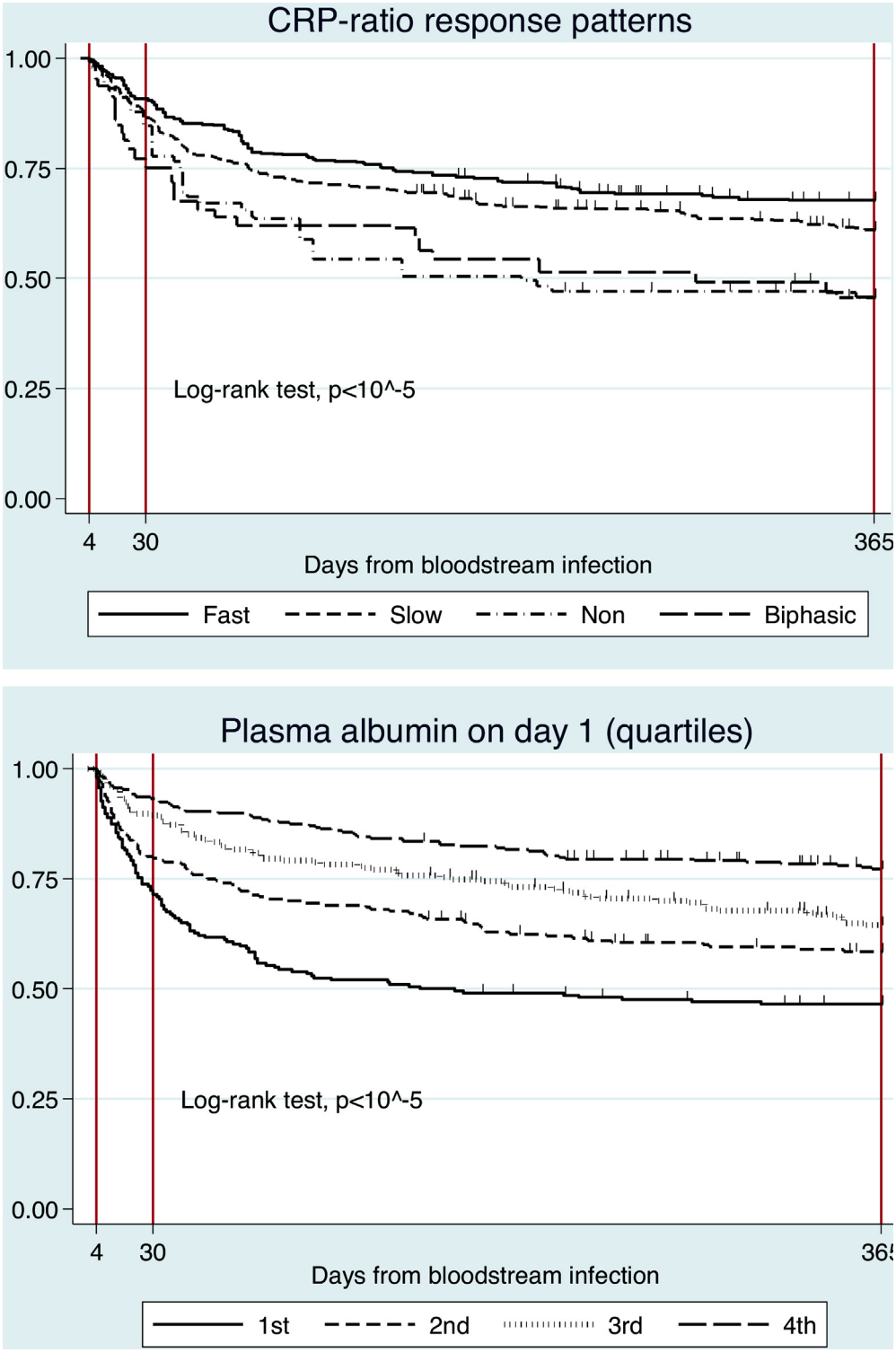

Figure 3. Kaplan–Meier mortality curves for C-reactive protein (CRP) ratio response patterns (upper panel) and quartiles of plasma albumin on day 1 (lower panel).

(Póvoa et al., 2005a). Several studies, comprising different infections and clinical settings, have assessed the prognostic value of individual patterns of CRP-ratio response to antibiotic therapy (Póvoa et al., 2005a, 2005b; Coelho et al., 2007; Moreno et al., 2010; Póvoa et al., 2011, 2017; Rabello et al., 2017). In all these studies, patients with a fast response pattern had much lower hospital mortality than those presenting with non-response or a biphasic response. But none of those studies assessed the impact of CRP-ratio patterns on long-term mortality.

In the present study we found that among patients alive on D4 the patterns of CRP-ratio response were associated with both short and long-term mortality, even after adjusting for clinically important confounders (Table 3). In comparison with those having a fast response pattern, patients with a non-response or a biphasic response patterns had a 2.5× and 5.0× increased risk, respectively, of death in D4–D30 and a 2.5× and 3.0× increased risk, respectively, of death in D31–D365.

Table 3
Logistic regression analyses.

Model	4–30 day mortality		31–365 day mortality	
	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
C-reactive protein ratio response				
Fast	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Slow	1.74 (1.14–2.67)[b]	1.75 (1.13–2.73)	1.47 (1.02–2.12)[b]	1.45 (0.98–2.13)
None	2.41 (1.21–4.79)	2.74 (1.32–5.68)	2.29 (1.17–4.48)	2.77 (1.34–5.74)
Biphasic	4.39 (2.34–8.23)	5.29 (2.67–10.5)	2.18 (1.08–4.40)	3.16 (1.46–6.84)
Plasma albumin on D1	0.90 (0.87–0.92)	0.90 (0.87–0.92)	0.95 (0.93–0.98)	0.94 (0.92–0.97)
C-reactive protein ratio response				
Fast	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Slow	1.71 (1.10–2.65)	1.68 (1.06–2.64)	1.50 (1.04–2.17)	1.46 (0.99–2.16)
None	3.22 (1.56–6.67)	3.00 (1.40–6.41)	2.55 (1.29–5.07)	2.90 (1.38–6.08)
Biphasic	3.56 (1.84–6.92)	4.29 (2.11–8.71)	2.06 (1.00–4.18)	2.95 (1.35–6.45)
Plasma albumin on D1	0.90 (0.87–0.93)	0.90 (0.87–0.93)	0.95 (0.93–0.98)	0.95 (0.92–0.97)

[a] Adjusted for gender, age, the Charlson comorbidity index (0, 1–2, >2 points), the main bacterial groups (mono-microbial gram-positive, mono-microbial gram-negative, poly-microbial), and number of organ dysfunctions (0, 1, >1).
[b] Odds ratio (95% confidence interval).

Table 4
Discrimination analyses, based on the logistic regression analyses.

Model	AUROC (95% CI)[a]	
	4–30 day mortality	31–365 day mortality
(1) C-reactive protein ratio response	0.61 (0.56–0.65)^{A}	0.57 (0.53–0.61)^{A}
(2) C-reactive protein ratio response, full model[b]	0.73 (0.69–0.77)^{BCD}	0.72 (0.68–0.76)^{B}
(3) Plasma albumin on day 1	0.70 (0.65–0.74)^{C}	0.59 (0.55–0.64)^{A}
(4) Plasma albumin on day 1, full model	0.77 (0.73–0.81)^{D}	0.72 (0.68–0.76)^{B}
(1) +3	0.74 (0.69–0.78)^{BD}	0.63 (0.58–0.67)^{C}
(2) +3	0.79 (0.75–0.82)^{E}	0.74 (0.70–0.78)^{B}

[a] Area under the receiver operating characteristic curve (95% confidence interval).
[b] The full model amends the following covariates: gender, age, the Charlson comorbidity index (0, 1–2, >2 points), the main bacterial groups (mono-microbial gram-positive, mono-microbial gram-negative, poly-microbial), and number of organ dysfunctions (0, 1, >1).Upper case letters: AUROC for models are significantly different ($p < 0.05$) if letters are different.

Several studies showed that the survivors of sepsis presenting persistent low-grade inflammation, assessed by elevations in circulating interleukin (IL) 6, IL-10, or CRP at the time of hospital discharge are associated with worse long-term outcomes (Kellum et al., 2007; Yende et al., 2008, 2014, 2019). The results of our study go somewhat beyond that as we show that a persistent inflammation measured as early as D4, assessed by CRP-ratio, is strongly correlated with both short and long term mortality.

The biological properties of PA differ from those of CRP, such as less variation in levels and a half-life of about 20 days (Franch-Arcas, 2001), in contrast to 19–20 h for CRP (Vigushin et al., 1993). As a result, the absence of marked changes of PA levels till D4 was an expected result. Similarly, it was not feasible to extrapolate the above four CRP-ratio response patterns to PA. Preliminarily, we derived a PA pattern based on only decreases, only increases, or both, between D1–D4, but these had no prognostic prediction, especially not when PA on D1 was incorporated in the models (data not shown).

The strong prognostic prediction of a bad outcome, both mortality and morbidity, in relation to a lower PA level is well-known (Vincent et al., 2003; Levitt and Levitt, 2016). In the present study, we divided patients in quartiles of PA on D1 and besides showing an impact on the D4–D30 mortality, this effect also had marked influence on the long-term mortality.

Finally, we assessed the ability of the CRP-ratio and PA on D1 to identify patients with poor short and long-term mortality. After adjusting for gender, age, Charlson comorbidity index, the main bacterial groups, and number of organ dysfunctions, the complete model presented an acceptable discriminative performance with an AUROC of 0.79 (Hosmer and Lemeshow, 2000).

To our knowledge, our study is the first to have combined CRP and PA as prognostic predictors in BSI patients. The combined use of CRP and PA has shown in numerous publications to be good a predictor of cancer-related mortality. Especially the Glasgow Prognostic Score (reviewed in McMillan, 2013) and the CRP/PA ratio (reviewed in Xu et al., 2017) have gained momentum. A few studies have combined CRP and PA as prognostic predictors in patients that may resemble BSI patients more than cancer patients. For 334 patients admitted to an ICU with sepsis or septic shock, Ranzani et al. showed that the CRP/PA ratio at admission or discharge predicted 90-day mortality (Ranzani et al., 2013). In 424 CA pneumonia patients, the amendment of initial CRP and PA levels to the pneumonia severity index improved the predictability of 28-day mortality, with an AUROC of 0.81, similar to our full model (Lee et al., 2011).

Our study has several strengths. To the best of our knowledge this is the study with the largest sample size of CA-BSI patients assessing serial measurements of CRP and PA. Secondly, our study is population-based and included clinically important data for comorbidity as well as the patients' septic conditions and vital organ dysfunctions around the time of the CA-BSI episode. And finally, for the first time the impact of the CRP-ratio patterns on the long-term mortality was assessed.

There are also several limitations that should be acknowledged. Firstly, it is a retrospective study although the data *per se* were prospectively collected from registries and medical records. Secondly, we had no information about the nutritional status. This is a concern in relation to whether PA is mainly a nutritional or inflammatory marker. Most reviews, including recent ones, imply that PA is a poor nutritional marker (Fuhrman, 2002; Lee et al., 2015;

Levitt and Levitt, 2016) and the sudden decline of the PA level around the CA-BSI as well as the high inverse correlation with the CRP level as seen in our study cohort (Gradel et al., 2018b) indicate that hypoalbuminemia is mainly an inflammatory marker. Thirdly, although we had microbiology results, we had no antibiotic sensitivity tests. As a result, we cannot evaluate the adequacy of empiric antibiotic therapy. Fourthly, we had no data on fluid therapy and fluid balance, including whether it contained albumin or plasma. However, neither albumin nor plasma are standard treatments to sepsis of BSI patients in OUH and our data on albumin vs. hemoglobin levels around the time of CA-BSI indicate that such data would not alter the interpretation of the results (Gradel et al., 2018b). Fifthly, roughly 50% of the CA-BSI patients were excluded from our study for three main reasons that impede the calculation of the D4 CRP-ratio; the CRP was not measured on D1 and D4, death occurred before D4, and the CRP levels were low on D1. The lack of data is a well-recognized limitation of studies using real-life data. Different patients present different numbers of specimens and highly variable time intervals between specimens. However, we have shown that the trajectories of CRP and PA levels around the CA-BSI (between day −30 and day 30) did not differ in relation to the number of specimens from each patient (Gradel et al., 2018a). Therefore, this would enable us to perform longitudinal analyses of real-life data in our population-based database. For the same reason, we could not also calculate CRP-ratio for patients who died before D4. We do know, however, that the mortality of BSI patients with high initial CRP levels is significantly higher (Gradel et al., 2011). Another important characteristic of a biomarker for longitudinal evaluation is amplitude of variation. If the values are very low or within "normal" range on D1, it is not possible to assess changes over time since some variations could be the result of the within-patient variation related to the measurement methodology (Póvoa et al., 2015). Sixthly, according to the CRP-ratio patterns of response, at least three measurements are needed to classify a biphasic pattern. As a result, patients with only two measurements could have been misclassified. However, the D4 CRP-ratio is above 80% in both a biphasic and a non-response pattern and both were associated with a poor prognosis (Póvoa et al., 2005a, 2005b, 2017). Finally, some of our CA-BSIs are healthcare-associated according to widely accepted definitions (Friedman et al., 2002) but we believe this has little impact on the patho-physiological properties of the studied biomarkers.

Conclusion

Serial CRP measurements after CA-BSI diagnosis are clinically useful as early as D4 to identify patients with a poor outcome. Besides, the identification of individual pattern of CRP-ratio response further refines our ability of prognostication either of short or long-term mortality. The addition of D1 PA further increases this ability. Patterns associated with persistent inflammation are associated with a higher short or long-term mortality.

Taken together these results confirm that serial measurements of biomarkers, like CRP, could be used not only for prognostication but also in antimicrobial stewardship programs (Borges et al., 2019), but further studies are needed.

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Ethics approval

According to the General Data Protection Regulation of the EU, implemented in Denmark in April 2018, no approval from the Danish Data Protection Agency is required. Approval by an ethics committee or consent from participants is not required for registry-based research in Denmark.

Declarations of interest

None.

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