Real-life data patterns of C-reactive protein and albumin level trajectories around bacteremia

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ABSTRACT

Aims
To assess trajectory patterns of C-reactive protein (CRP) and plasma albumin (PA) levels around bacteraemia.

Patients & Methods
Population-based study, 2,418 community-acquired bacteraemia patients, CRP and PA specimens from 30 days before through 30 days after bacteraemia (day 0). A pattern was based on specimen occurring or not in days −30/−1, 0, 1/7, or 8/30. Mean daily CRP and PA levels on day −30/30 were computed for pattern subgroups.

Results and Conclusions
Mean CRP rose on day −5 and reached its peak on day 1. Mean steady PA on day −30/0 declined abruptly on day 1, increasing slowly thereafter. Trajectories did not differ between subgroups. We conclude that longitudinal analysis results can be extrapolated to all community-acquired bacteraemia patients.
Executive summary

Background:
- No study has assessed trajectories of C-reactive protein (CRP) and plasma albumin (PA) levels in real-life data around bacteraemia

Methods and main results:
- CRP and PA specimens from 30 days before through 30 days after bacteraemia (day 0)
- A pattern based on specimen occurrence (yes/no) in four periods (day −30/−1, 0, 1/7, 8/30)
- Trajectories, based on mean daily CRP and PA levels on day −30/30, were computed for pattern subgroups
- Trajectories did not differ between pattern subgroups
- 30-day mortality odds ratios for age, gender, comorbidity, bacteria group, sepsis status, and albumin level did not change materially when amending 0 vs. ≥1 specimen in day −30/0 to the multivariate model, though the latter had 50% higher mortality

Conclusion:
- Trajectories of CRP and PA levels around bacteraemia did not differ in relation to number of specimens from each patient. This enables longitudinal analyses of real-life data in population-based studies

Key words
Bacteraemia, community-acquisition, C-reactive protein, plasma albumin, daily mean level trajectories
Introduction

The unique personal identifier given to all residents in Scandinavian countries enables merging between administrative health registries, in which the main advantages include the reporting of population-based results and high statistical precision due to large number of patients [1-3]. However, the amount of data from administrative registries is highly correlated to clinical indications, such as increasing numbers of biochemical specimens in sicker patients. Thus, caveat is prudent due to possible confounding by indication.

We have previously reported the prognostic prediction of one-time levels of serum C-reactive protein (CRP) [4, 5] and plasma albumin (PA) [6] in community-acquired bacteraemia patients from a geographically well-defined Danish region. In the same cohort, we recently found that levels of CRP and PA were inversely correlated before, during and after the bacteraemic episode, even after adjustment for other clinically important cofounders such as sepsis criteria or organ dysfunctions [7]. The major limitations of that retrospective cohort study were the different numbers of specimens (ranging from 1 to 674 per patient) and the highly variable time intervals between specimens. Although sophisticated statistical methods may partly compensate for such imbalances [8] we still believed that such a heterogeneous specimen pattern precluded longitudinal data analyses (two or more specimens at different time points) for the whole study cohort.

The ideal study cohort should thus have the same number of biochemical specimens with equal time intervals between all specimens (as in well-designed prospective studies) while not compromising the population-based principles. In this study we ultimately aimed to assess whether results from one or more subgroups, having a more homogenous specimen pattern, could be extrapolated to the more heterogeneous study cohort. Consequently, we opted to select such subgroups among adult community-acquired bacteraemia patients incorporating CRP and PA levels measured from 30 days before (day −30) through 30 days after (day 30) the bacteraemia date. There were three specific aims of this study: i) to derive subgroups according to specimen patterns in day −30/30; ii) for all subgroups, to compute daily mean levels with 95% confidence intervals (CIs) of CRP and PA in day −30/30 to evaluate whether they followed the same trajectories; iii) in multivariate analyses, to assess the impact of specimen pattern subgroup up to and including the bacteraemia date, on 30-day mortality.
Patients and Methods

Setting

The Danish public health system is tax financed and free of charge for all residents. The admission of all Funen County residents with acute illness to a hospital within the county prompted a population-based design.

Analyses of CRP and PA levels

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

Derivation of the initial study cohort

The study cohort has been described previously [4-7]. In brief, it comprised all adult (>14 y) persons residing in the Funen County with their first-time community-acquired bacteraemia in 2000-2008, and CRP measured from two days before until the day after the bacteraemia date (date of draw of blood culture [BC]; if date of draw was missing, date of receipt of BC [never missing]). The bacteraemia was community-acquired if the bacteraemia date occurred <3 days after hospital admission and there was no inpatient contact in the seven days up to the bacteraemia date. We had all measurements of CRP and PA from 1 January 2000 through 30 September 2010 [7], but excluded unrealistically low levels of PA (<11 g/L) and maintained one measurement only for each parameter on the same date (for PA the lowest level and for CRP the highest), computing a specimen date as the analytical unit.

Derivation of the final study cohort

We included only specimen dates on which both PA and CRP were measured and occurring from 30 days before through 30 days after the bacteraemia date.

Computation of periods in relation to the bacteraemia date

Please refer to Table 1 and the supplementary figure for further details. Within a time span from 30 days before through 30 days after the bacteraemia date (designated day 0) we computed the following four periods: i) day −30 to −1; ii) day 0; iii) day 1-7; iv) day 8-30. For each patient we
marked whether one or more specimen dates occurred in each of these four periods (1 if yes, 0 if no) and computed a specimen pattern for all four periods, e.g. 1-1-0-0 if ≥1 specimen date occurred in each of the periods i) and ii) and no specimen dates occurred in period iii) or iv). For each specimen pattern we computed the number (%) of patients dying within 30 days after day 0.

Subgroups pertaining to specimen dates within the first two periods

Among the 15 specimen patterns (“ranging from” 0-0-0-1 to 1-1-1-1) we selected subgroups depending on whether specimen dates occurred in period i) and/or ii) (Table 1). Because the occurrence of specimen dates in periods iii) (day 1-7) and iv) (day 8-30) depended on the death of the patient within these periods (unequal risk time of having a specimen taken) we did not derive subgroups according to specimen patterns in these two periods.

Daily mean CRP and PA levels during relevant periods according to subgroups

In order to assess whether trajectories followed similar patterns we determined initially that the specimen pattern 1-1-1-1 (i.e. ≥1 specimen date in each period, Table 1) represented a gold standard trajectory. For each of the following subgroups we graphically depicted daily mean levels with 95% CIs of CRP and PA within the relevant periods i)–iv): i0, i1 (excluding pattern 1-1-1-1), pattern 1-1-1-1, i0ii0, i0ii1, i1ii0, i1ii1, ii0, and ii1 (Table 1). Because trajectories for all these subgroups were very similar we only show graphs for the first three groups (Figures 1 and 2). For all subgroups we reiterated the graphic depictions by including only the first or the last specimen within each relevant period.

30-day mortality analyses

We used logistic regression analyses with odds ratios (ORs) and 95% CIs, with mortality within 30 days from the bacteraemia date as the outcome. Initially, we adopted the predisposition-insult-response-organ dysfunction (PIRO) model [9] used previously [6]. We included age, gender, Charlson comorbidity index (0, 1, and ≥2 points) [10], main bacterial groups (Gram-positive, Gram-negative, and polymicrobial), and sepsis severity groups (no sepsis, possible sepsis, sepsis, severe sepsis/septic shock, and organ dysfunction without sepsis) [4-7] as covariates in one baseline model. In a second baseline model we further included the PA level on day 0 as a covariate. Referring to Table 1, we incorporated subgroups i0 (reference) vs. i1, i0ii0 vs. i0ii1, i1ii0/i1ii1 vs. i1ii1, and ii0 (reference) vs. ii1 in both baseline models. In addition to assessing the ORs (95% CIs) for the day 0 PA level and the said subgroups we evaluated
the degree of which the inclusion of these covariates altered ORs for the baseline model covariates.

Software used for the analyses

We used the program Stata®, vs. 14 (StataCorp, College Station, TX, USA) for all analyses.

Ethical considerations

The study was conducted according to the guidelines of the regional scientific ethics committee for use of clinical and laboratory data and approved by the Danish Data Protection Agency (record no. 2013-41-2579).
Results

Specimen patterns

Four of the 15 specimen patterns occurred in >10% of the patients: pattern 0-1-1-1 in 693/2,418 patients (28.7%), 0-1-1-0 in 425 patients (17.6%), 0-0-1-1 in 300 patients (12.4%), and 1-1-1-1 in 250 patients (10.3%) (Table 1). Subgroup i0, in which no specimens were retrieved up to 30 days before the bacteraemia date, comprised 1,878 patients (77.7%). In subgroup i0, 1,366 patients (72.7%, subgroup i0ii1 in Table 1) had a specimen retrieved on day 0, whereas in subgroup i1 this was the case for 420 patients (77.8%, subgroup i1ii1 in Table 1).

Numbers of specimen dates

A total of 2,418 patients had 18,434 specimen dates on which both CRP and PA levels were measured. There were 1,673 (9.1%) specimen dates in period i), 1,786 (9.7%) in period ii), 7,225 (39.2%) in period iii), and 7,750 (42.0%) in period iv). Each patient had from 1 to 50 specimen dates (mean [sd] was 7.6 [6.9], median was 6), which also reflected the high variation within each of the three periods i), iii) and iv) (Table 2). Among the 250 patients with the pattern 1-1-1-1, the number of specimen dates ranged from 4 to 50, the mean (sd) was 14.9 (8.3) and the median was 13.

Daily mean CRP and PA levels according to subgroups

All trajectories followed the overall patterns reported earlier [7] and are briefly described here: Mean CRP levels declined from day −20 to day −5, increased until day 1, and declined again to the pre-bacteraemic level on day 15 (Figure 1). The mean PA levels were steady before day 1, declined suddenly on day 1, and increased on day 15-30, not reaching the pre-bacteraemic level though, with the only exception that the decline for specimen pattern 1-1-1-1 was more gradual from day −2 through day 1 (Figure 2). CRP and PA trajectories for subgroups not shown in Figures 1 and 2 (subgroups i0i0, i0i1, i1i0, i1ii1, i0i, ii1) were materially the same. The same applied to trajectories reiterated with either the first or the last specimen in relevant periods, except that some subgroups (i1ii0, i0, and, for the first CRP measurement, also i1ii1) had such low numbers that depiction of daily mean levels and their very wide CIs made no sense (data not shown).

30-day mortality according to specimen pattern

30-day mortality could be computed for 2,417 of the 2,418 patients (one patient emigrated before day 0). Amongst these, 492 patients (20.4%) died within 30 days after day 0 (Table 1). This
percentage differed considerably between specimen pattern groups, ranging from 0% for specimen pattern 1-0-0-1 to 69.4% for specimen pattern 1-1-0-0 (Table 1). It was mainly the specimen patterns in periods iii (day 1-7) and iv (day 8-30) that were associated with 30-day mortality, which was higher if no specimens were retrieved in these periods.

**Multivariate 30-day mortality analyses**

In the baseline PIRO model without adjustment for PA on day 0, higher age, Charlson comorbidity index ≥2, polymicrobial bacteraemia, severe sepsis, and organ dysfunction without sepsis were positively associated with 30-day mortality, whereas Gram-negative mono-microbial bacteraemia predicted a lower 30-day mortality (data not shown). The PA level on the bacteraemia date was inversely associated with 30-day mortality (OR [95% CI]: 0.88 [0.86-0.90] per 1 g/L) and its amendment to the baseline model altered ORs (95% CIs) for males from 1.16 (0.94-1.44) to 1.40 (1.07-1.82), annulled the significant prediction of 30-day mortality for polymicrobial bacteraemia and organ dysfunction without sepsis, and reduced the ORs for Charlson indices 1 and ≥2 (data not shown).

All ORs (95% CIs) in the two baseline models remained virtually unaltered after subgroups (i0 vs i1, i0ii0 vs. i0ii1 vs. i1ii0 vs. i1ii1, i0ii0/i0ii1/i1ii0 vs. i1ii1, ii0 vs. ii1) were amended (data not shown).

In models amending subgroups i0 and i1, subgroup i1 (i.e. ≥1 specimen date in day −30/−1) predicted higher 30-day mortality, both without (OR [95% CI]: 1.58 [1.23-2.04]) and with PA (1.48 [1.09-2.01]) in the model (Table 3).

Further model evaluations, including subgroups i0ii0, i0ii1 (reference), i1ii0, and i1ii1 as well as i0ii0/i0ii1/i1ii0 (reference) and i1ii1, elucidated that it was mainly subgroup i1ii1 (i.e. ≥1 specimen date in day −30/−1 and a specimen on day 0) that predicted higher 30-day mortality and the ORs (95% CIs) were virtually the same as for subgroup i1. In contrast, whether CRP/PA was or was not measured on the date of bacteraemia (subgroup ii0 vs. subgroup ii1) was not associated with 30-day mortality (OR [95% CI]: 1.19 [0.93-1.52]).
Discussion

As expected, for real-life data in which clinical indication and short-time survival were important determinants for the retrieval of specimens, we found a highly heterogeneous specimen pattern from 30 days before through 30 days after the bacteraemia date. However, subgroups computed according to whether specimens were retrieved in the 30 days preceding the bacteraemia date and/or on the bacteraemia date had very similar trajectories of CRP and PA levels before, on, and after the bacteraemia date. This indicates that pathophysiological mechanisms were the same regardless of the patients’ frailty. In order to equalize each patient’s contribution to the mean CRP and PA levels within each time period we reiterated the mean level trajectories using either the first or the last specimen within each period. This, however, did not alter the trajectories indicating that the impact on the trajectories from patients with higher numbers of specimens was minor. The main difference between these subgroups was found in a 50% higher 30-day adjusted mortality if patients had one or more CRP/PA specimens retrieved in the 30 days preceding the bacteraemia date. We interpret this as a proxy marker of comorbidity and/or inflammation prior to bacteraemia and as such a prognostic amendment to the Charlson comorbidity index incorporated in the baseline PIRO model.

To the best of our knowledge this is the first study that has used real-life data to assess specimen patterns around the time of bacteraemia. Whereas most of the bacteraemia patients had CRP and PA specimens retrieved when bacteraemia was suspected, only 22.3% had at least one specimen retrieved during the preceding 30 days. However, 420 of these 540 patients (77.8%) also had a specimen retrieved on the bacteraemia date, i.e. patients with the specimen pattern 1-1-X-X. This is probably the subgroup for which longitudinal data analyses incorporating levels and changes of both CRP and PA is most feasible. Due to the high similarities between trajectories the results from such analyses can be extrapolated to our entire study cohort.

CRP is unequivocally interpreted as an inflammation marker, whereas possible causes of hypoalbuminaemia are more prone to discussion [11-18]. The main distinction relates to whether hypoalbuminaemia represents a chronic condition (e.g. liver failure, malnutrition, or chronic inflammation) or an acute inflammation [16]. To further elucidate this, studies of longitudinal PA measurements are required, in particular to evaluate changes in relation to an acute inflammation as encountered in bacteraemia. The long half-life of PA of about 20 days [11] indicates that a de-
cline in the PA level within a few days represents an acute condition. Results from numerous stud-
ies, also found for this cohort [6], have unanimously concluded that hypoalbuminaemia is associ-
ated with an unfavourable prognosis (reviewed in [19]). Virtually all of this review’s 90 studies in-
cluded only a single PA level as a prognostic predictor even though half of the studies were pro-
spective. Only a few studies have incorporated longitudinal PA level measurements, mainly in pro-
spective studies [20-27], but none of these prognostic studies dealt with PA levels or changes in
relation to chronic vs. acute conditions. Changes in blood parameter levels may be more discrimi-
natory than single measurements, e.g. as reported for CRP as a mortality predictor [28], but less is
known as to whether this also applies to other outcomes than mortality or to PA.

The main strengths of this study include the population-based study cohort, patients with a
clearly defined acute inflammatory condition based on generally accepted criteria [29, 30] (i.e.
bacteraemia), data on comorbidity (representing the more chronic conditions), clinically important
data (on sepsis and organ dysfunction at the time of bacteraemia), and high numbers of patients
and specimens.

Our study also has limitations that warrant further discussion. The first and main limitation,
confounding by indication, was the main reason for conducting this study. Secondly, we had no
nutrition data (e.g., subjective global assessment score [31], anthropometry [32], or equilibrated
normalized protein catabolic rate anthropomorphic [20]), which could be important confounders
in our multivariate models in light of the discussion on what the PA levels and changes represent
[16]. Thirdly, general practitioners (GPs) either submit CRP specimens to the Department of Clini-
cal Biochemistry and Pharmacology, OUH, for analysis or they analyse the specimens themselves.
As we do not have access to the GPs own analyses we do not know how many of such specimens
we have missed. Probably, some GPs submit all their specimens, others analyse all of them in their
clinic, while others, to get an immediate result, only choose the latter option for acutely ill pa-
tients. The inclusion of such specimen would thus contribute to the heterogeneity of our study
cohort, but we believe it is unlikely that they would materially change the trajectories. As far as we
know, no PA specimens are analysed by the GPs themselves. Finally, our time periods are open for
discussion. We reckoned that the 30 days preceding the bacteraemia date would suffice to include
relevant events that led up to the bacteraemic episode. Likewise, the first week after the bacte-
raemic episode represented the most acute conditions, which would wane in the 8-30 day period.
Although these cut-off values are not globally defined or accepted the consistent findings indicate that other cut-off values would probably not alter our results materially.

In conclusion, the consistent results indicate that further studies incorporating cross-sectional CRP and PA levels as well as their changes to deduce mutual correlations and prognostic aspects are feasible and subgroup analysis results can be extrapolated to subgroups with a different specimen pattern. To distinguish between intra- and inter-patient variation, such studies will have to incorporate longitudinal and multi-level data analyses [8].
References

Papers of special note have been highlighted as:

* of interest ** of considerable interest

1 Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur. J. Epidemiol.* 29(8), 541-549 (2014).


* This review gives an excellent overview of pathophysiological mechanisms related to hypoaalbuminaemia


** An inverse correlation between albumin and CRP levels, shown longitudinally, is seen in chronic renal failure patients. This review summarizes, amongst others, ref. 20-24.


** Hypoaalbuminaemia is associated with an increased interstitial distribution space, whereas serum albumin is not a good indicator of nutrition.


** Longitudinal correlations between albumin and CRP levels are evaluated in 97 CAP patients, including in the remission period.

Table 1:
Specimen patterns according to whether one or more specimens were retrieved in each of four periods, for 2,418 patients with their first-time community-acquired bacteraemia

<table>
<thead>
<tr>
<th>Specimen pattern (i-ii-iii-iv)</th>
<th>Period, days (designation)</th>
<th>No. patients (%)</th>
<th>Dead within 30 d (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>−30/−1</td>
<td>−30/−1</td>
<td>−30/0</td>
</tr>
<tr>
<td>i0 i0ii0 ii0 ii0</td>
<td>i0 i0ii0 ii0 ii0</td>
<td>18 (0.7)</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>i0 i0ii1 ii1 ii1</td>
<td>i0 i0ii1 ii1 ii1</td>
<td>300 (12.4)</td>
<td>29 (9.7)</td>
</tr>
<tr>
<td>i0 i0ii1 ii1 ii1</td>
<td>i0 i0ii1 ii1 ii1</td>
<td>195 (8.1)</td>
<td>71 (36.4)</td>
</tr>
<tr>
<td>i0 i0ii1 ii1 ii1</td>
<td>i0 i0ii1 ii1 ii1</td>
<td>53 (2.2)</td>
<td>3 (5.7)</td>
</tr>
<tr>
<td>i0 i0ii1 ii1 ii1</td>
<td>i0 i0ii1 ii1 ii1</td>
<td>425 (17.6)</td>
<td>118 (27.8)</td>
</tr>
<tr>
<td>i0 i0ii1 ii1 ii1</td>
<td>i0 i0ii1 ii1 ii1</td>
<td>693 (28.7)</td>
<td>75 (10.8)</td>
</tr>
<tr>
<td>i1 i1ii0 ii0 ii0</td>
<td>i1 i1ii0 ii0 ii0</td>
<td>18 (0.7)</td>
<td>9 (50.0)</td>
</tr>
<tr>
<td>i1 i1ii0 ii0 ii0</td>
<td>i1 i1ii0 ii0 ii0</td>
<td>5 (0.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>i1 i1ii0 ii0 ii0</td>
<td>i1 i1ii0 ii0 ii0</td>
<td>27 (1.1)</td>
<td>10 (37.0)</td>
</tr>
<tr>
<td>i1 i1ii0 ii0 ii0</td>
<td>i1 i1ii0 ii0 ii0</td>
<td>70 (2.9)</td>
<td>7 (10.0)</td>
</tr>
<tr>
<td>i1 i1ii0 ii0 ii0</td>
<td>i1 i1ii0 ii0 ii0</td>
<td>49 (2.0)</td>
<td>34 (69.4)</td>
</tr>
<tr>
<td>i1 i1ii0 ii0 ii0</td>
<td>i1 i1ii0 ii0 ii0</td>
<td>15 (0.6)</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>i1 i1ii0 ii0 ii0</td>
<td>i1 i1ii0 ii0 ii0</td>
<td>106 (4.4)</td>
<td>40 (37.7)</td>
</tr>
<tr>
<td>i1 i1ii0 ii0 ii0</td>
<td>i1 i1ii0 ii0 ii0</td>
<td>250 (10.3)</td>
<td>38 (15.2)</td>
</tr>
</tbody>
</table>

All 2,418 (100) 492 (20.4) |

1 Four periods: i) from 30 days through 1 day before the bacteraemia date (day 0); ii) on day 0; iii) 1-7 days after day 0; iv) 8-30 days after day 0
2 0 if no specimens were retrieved, 1 if ≥1 specimens were retrieved, each pattern representing the four periods chronologically
3 Each subgroup derived according to whether specimens were retrieved (0 or 1, cf. footnote 2) in the specified period
4 75/692, because 1 patient emigrated before his bacteraemia date
5 492/2,417, cf. footnote 4
Table 2:
Distribution of number of specimen dates per patient, for periods i) (30–1 days before the bacteraemia date), iii) (1–7 days after the bacteraemia date), and iv) (8–30 days after the bacteraemia date)

<table>
<thead>
<tr>
<th>No. specimen dates per patient</th>
<th>Period i) (day −30/−1)</th>
<th>Period iii) (day 1–7)</th>
<th>Period iv) (day 8–30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>249 (46.1)</td>
<td>406 (19.7)</td>
<td>336 (23.9)</td>
</tr>
<tr>
<td>2</td>
<td>97 (18.0)</td>
<td>404 (19.6)</td>
<td>191 (13.6)</td>
</tr>
<tr>
<td>3</td>
<td>54 (10.0)</td>
<td>333 (16.1)</td>
<td>160 (11.4)</td>
</tr>
<tr>
<td>4</td>
<td>31 (5.7)</td>
<td>275 (13.3)</td>
<td>116 (8.3)</td>
</tr>
<tr>
<td>5</td>
<td>29 (5.4)</td>
<td>209 (10.1)</td>
<td>84 (6.0)</td>
</tr>
<tr>
<td>6</td>
<td>22 (4.1)</td>
<td>199 (9.6)</td>
<td>82 (5.8)</td>
</tr>
<tr>
<td>7</td>
<td>12 (2.2)</td>
<td>239 (11.6)</td>
<td>74 (5.3)</td>
</tr>
<tr>
<td>8</td>
<td>7 (1.3)</td>
<td>-</td>
<td>57 (4.1)</td>
</tr>
<tr>
<td>9</td>
<td>6 (1.1)</td>
<td>-</td>
<td>59 (4.2)</td>
</tr>
<tr>
<td>10</td>
<td>8 (1.5)</td>
<td>-</td>
<td>32 (2.3)</td>
</tr>
<tr>
<td>11</td>
<td>3 (0.6)</td>
<td>-</td>
<td>31 (2.2)</td>
</tr>
<tr>
<td>12</td>
<td>4 (0.7)</td>
<td>-</td>
<td>35 (2.5)</td>
</tr>
<tr>
<td>13-30</td>
<td>18 (3.3)</td>
<td>-</td>
<td>147 (10.5)</td>
</tr>
<tr>
<td>All</td>
<td>540 (100)</td>
<td>2,065 (100)</td>
<td>1,404 (100)</td>
</tr>
</tbody>
</table>

1 Number of patients (%)
Table 3:
Odds ratios (95% confidence intervals) in predisposition-insult-response-organ dysfunction (PIRO) logistic regression models, 30-day mortality as outcome, without and with adjustment for serum albumin on the bacteraemia date (alb), with adjustment for subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Model</th>
<th>PIRO/grp¹</th>
<th>PIRO/grp/alb²</th>
</tr>
</thead>
<tbody>
<tr>
<td>i0</td>
<td>1 (ref.)</td>
<td>1 (ref.)</td>
<td></td>
</tr>
<tr>
<td>i1</td>
<td><strong>1.58 (1.23-2.04)</strong></td>
<td>1.48 (1.09-2.01)</td>
<td></td>
</tr>
<tr>
<td>i0i0</td>
<td>0.91 (0.69-1.21)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>i0i1</td>
<td>1 (ref.)</td>
<td>1 (ref.)</td>
<td></td>
</tr>
<tr>
<td>i1i0</td>
<td>1.18 (0.72-1.92)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>i1i1</td>
<td><strong>1.66 (1.25-2.20)</strong></td>
<td>1.48 (1.09-2.01)</td>
<td></td>
</tr>
<tr>
<td>i0i0/i1i0/i0i1i1</td>
<td>1 (ref.)</td>
<td>1 (ref.)</td>
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<td><strong>1.68 (1.28-2.19)</strong></td>
<td>1.48 (1.09-2.01)</td>
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<td>1 (ref.)</td>
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<td>ii1</td>
<td>1.19 (0.93-1.52)</td>
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¹ Models without albumin on the bacteraemia date include 2,417 community-acquired bacteraemia patients (1 patient emigrated before his bacteraemia date). Adjusted for age, gender, Charlson comorbidity index (0, 1, and ≥2 points), main bacterial groups (Gram-positive, Gram-negative, and polymicrobial), and sepsis severity groups (no sepsis, possible sepsis, sepsis, severe sepsis/septic shock, and organ dysfunction without sepsis)

² Models with serum albumin on the bacteraemia date (in addition to covariates in foot note 1) include 1,785 community-acquired bacteraemia patients

³ See Table 1

* Bold: significant odds ratios
Figure captions

Figure 1
Daily mean levels (95 % confidence intervals) in mg/L of C-reactive protein, for patients with ≥1 specimen date in each of four periods (30-1 days before day 0 [designated day −30/−1], day 0 [the bacteraemia date], day 1-7, and day 8-30) (upper panel), for patients with ≥1 specimen date in day −30/−1, but excluding patients from the upper panel (middle panel), and for patients with no specimen dates in day −30/−1 (lower panel). All panels cover day −30/30.

Figure 2
Daily mean levels (95 % confidence intervals) in g/L of plasma albumin, for patients with ≥1 specimen date in each of four periods (30-1 days before day 0 [designated day −30/−1], day 0 [the bacteraemia date], day 1-7, and day 8-30) (upper panel), for patients with ≥1 specimen date in day −30/−1, but excluding patients from the upper panel (middle panel), and for patients with no specimen dates in day −30/−1 (lower panel). All panels cover day −30/30. Note the lowest y-axis value of 24 g/L.
Figure 1

Figure 2
**Supplementary figure:**

Illustration of specimen patterns in four periods (0 if no specimens, 1 if ≥1 specimens were retrieved)

<table>
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<th>30/1 days before bacteraemia</th>
<th>Day 0 (day of bacteraemia)</th>
<th>1/7 days after bacteraemia</th>
<th>8/30 days after bacteraemia</th>
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