Stability in community-acquired pneumonia: one step forward with markers?

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ABSTRACT

Background: Biological markers as an expression of systemic inflammation have been recognised as useful for evaluating the host response in community-acquired pneumonia (CAP). The objective of this study was to evaluate whether the biological markers procalcitonin (PCT) and C-reactive protein (CRP) might reflect stability after 72 h of treatment and the absence of subsequent severe complications.

Methods: A prospective cohort study was performed in 394 hospitalised patients with CAP. Clinical stability was evaluated using modified Halm's criteria: temperature $\leqslant$37.2°C; heart rate $\leqslant$100 beats/min; respiratory rate $\leqslant$24 breaths/min; systolic blood pressure $\geqslant$90 mm Hg; oxygen saturation $\geqslant$90%; or arterial oxygen tension $\geqslant$60 mm Hg. PCT and CRP levels were measured on day 1 and after 72 h. Severe complications were defined as mechanical ventilation, shock and/or intensive care unit (ICU) admission, or death after 72 h of treatment.

Results: 220 patients achieved clinical stability at 72 h and had significantly lower levels of CRP (4.2 vs 7 mg/dl) and of PCT (0.33 vs 0.48 ng/ml). Regression logistic analyses were performed to calculate several areas under the ROC curve (AUC) to predict severe complications. The AUC for clinical stability was 0.77, 0.84 when CRP was added ($p = 0.059$) and 0.77 when PCT was added ($p = 0.45$). When clinical stability was achieved within 72 h and marker levels were below the cut-off points (0.25 ng/ml for PCT and 3 mg/dl for CRP), no severe complications occurred.

Conclusions: Low levels of CRP and PCT at 72 h in addition to clinical criteria might improve the prediction of absence of severe complications.

Prognostic scales provide key information on predicting mortality, but this information is insufficient for assessing the response to antibiotic treatment and clinical stability.[1] The concept of clinical stability is very important for the clinician since it allows decision-making concerning hospital discharge and treatment length. The publication of stability clinical criteria by Halm *et al*[2] provided a fundamental basis to define this concept which has already been included in guidelines.[3] Nevertheless, clinical criteria are sometimes difficult to evaluate in elderly patients with low clinical expression, multiple associated diseases or with chronic respiratory insufficiency. Because of this, it would be of great value to have objective and easily measurable data to indicate "biological stability".

Markers such as C-reactive protein (CRP) and procalcitonin (PCT) have been used to quantify severity, systemic inflammation and prognosis.[4–9] It has been observed that an increase in markers and cytokines within 72 h of admission to hospital is associated with treatment failure and a poor outcome.[1] Furthermore, a reduction in these levels is associated with a good response.[1 8 9] An interesting perspective would be to evaluate the usefulness of markers in providing information on the resolution of the degree of inflammation after antibiotic treatment. It is known that 72 h after adequate treatment the concentration of microorganisms is dramatically reduced[10] and clinical stability is then reached.[2 11] Our hypothesis is that, when clinical stability is reached, the reduction in the markers is larger due to the fact that systemic inflammation is at a low safe level for the patient. If this can be demonstrated, levels of systemic markers could be used either on their own or jointly with clinical criteria of stability to decide safely whether there is a subsequent risk for the patient.

The objectives of this study are (1) to investigate if there is a correlation between clinical stability and levels of biological markers; (2) to evaluate whether biomarkers and/or assessment of clinical stability criteria can predict the absence of severe complications; and (3) to find or define the best cut-off points for PCT and CRP which enable the absence of severe complications or a poor prognosis after 72 h of antibiotic treatment to be identified.

METHODS

Patients

A prospective longitudinal study was conducted in patients with CAP consecutively admitted to two tertiary care teaching hospitals from October 2003 to June 2004. Inclusion criteria were a new radiographic infiltrate compatible with the presence of acute pneumonia and at least two signs or symptoms of CAP (eg, temperature >38°C, productive cough, chest pain, shortness of breath, crackles on auscultation). Exclusion criteria were admission within the previous 15 days, nursing home patients, immunosuppressive treatment and/or steroids (>15 mg/day), leucocyte count <1000/mm^3 or neutrophil count <500/mm^3 (except if attributable to CAP).

Data collection

Data on age, gender, smoking and alcohol habits (>80 g/day), prior influenza vaccination with that year's trivalent inactivated influenza vaccine before developing pneumonia, comorbid diseases such as chronic obstructive pulmonary disease, and cardiac, liver, renal or central nervous system disorders were collected. Recorded clinical signs and

symptoms were: cough, expectoration, pleuritic chest pain, dyspnoea, acute confusion, temperature, respiratory and heart rates, systolic and diastolic blood pressure and the presence of rales. The following analytical data were recorded: leucocyte count, sodium, potassium, serum creatinine, ALT/AST and arterial blood gas analysis. On admission, Fine risk classes[12] and CURB-65 were also recorded.[13] Initial empirical antimicrobial treatment was recorded and classified as follows: β-lactam (ceftriaxone/cefotaxime or co-amoxi-clavulanate) with a macrolide (clarithromycin or azithromycin), fluoroquinolone (levofloxacin), β-lactam with quinolone, β-lactam as monotherapy and other regimens. Surviving patients underwent radiological and serological follow-up after 30 days.

Definitions

Clinical stability was defined following a slight modification of Halm's criteria[2 11] as the condition when the following threshold values were achieved *for all parameters*: temperature $\leqslant$37.2 °C, heart rate $\leqslant$100 beats/min, respiratory rate $\leqslant$24 breaths/min, systolic blood pressure $\geqslant$90 mm Hg and oxygen saturation $\geqslant$90% or arterial oxygen tension $\geqslant$60 mm Hg when the patient was not receiving supplemental oxygen. In patients on home oxygen therapy, stability was considered to be achieved when their oxygen needs were the same as those before admission.

The primary outcome—severe complications after 72 h of treatment—was defined as death after 72 h of treatment and within 30 days of admission; shock or need for mechanical ventilation (invasive or non-invasive); or admission to the ICU after 72 h of treatment.

Determination of cytokines, PCT and CRP

Blood samples were drawn on the first day and centrifuged, coded and frozen at −80°C until subsequent analyses. Determination of interleukin (IL)-6, IL-8, IL-10 and tumour necrosis factor α (TNFα) was performed with a commercial enzyme immunoassay technique (Biosource, Nivelles, Belgium). Limits of detection were 3 pg/ml for TNFα, 2 pg/ml for IL-6, 0.7 pg/ml for IL-8 and 1 pg/ml for IL-10. An immunoluminometric technique was used to measure PCT (Liaison Bhams PCT, DiaSorin, Saluggia, Italy) with a detection limit of 0.3 ng/ml. CRP was measured with an immunoturbidimetric method using a commercially available test (Bayer Diagnostics) with an Advia 2400 (detection limit 1.5 mg/dl).

Statistical analysis

Statistical analysis was performed using SPSS Version 15.0 software. The χ^2 test was used for qualitative variables and the Student *t* test or Mann-Whitney U test for quantitative variables. Correlation was analysed using Spearman rho correlation analysis.

Several multivariate logistic regression analyses were performed to predict the absence of severe complications after day

Table 1 Characteristics, comorbidity and initial severity, and clinical stability

	Stability		
	⩽3 days	>3 days	
Characteristics	**n = 220 (55.8%)**	**n = 174 (44.2%)**	**p Value**
Mean (SD) age (years)	65 (17)	67 (18)	0.2
F/M (%)	76/144 (34.5/65.5)	72/102 (41.4/58.6)	0.1
Current smokers, n (%)	46 (20.9)	44 (25.3)	0.3
Excessive alcohol consumption, n (%)	25 (11.4)	21 (12.1)	0.8
Prior influenza vaccination, n (%)	98 (44.5)	66 (37.9)	0.2
Coexisting illnesses, n (%)			
Cardiac insufficiency	40 (18.2)	25 (14.4)	0.3
Renal insufficiency	12 (5.5)	8 (4.6)	0.7
Diabetes	49 (22.3)	29 (16.7)	0.1
Liver disease	5 (2.3)	6 (3.4)	0.4
COPD	39 (17.7)	31 (17.8)	0.9
Neurological disease	38 (17.3)	31 (17.8)	0.8
PSI, n (%)			
I	32 (14.5)	15 (8.6)	0.07
II	42 (19.1)	28 (16.1)	0.4
III	49 (22.3)	39 (22.4)	0.9
IV	79 (35.9)	63 (36.2)	0.9
V	18 (8.2)	29 (16.7)	0.01
CURB-65, n (%)			
0	41 (18.6)	22 (12.6)	0.1
1	84 (38.2)	48 (27.6)	0.1
2	55 (25.0)	54 (31.0)	0.1
3	32 (14.5)	34 (19.4)	0.1
4	8 (3.6)	14 (8.0)	0.06
5	0	2 (1.1)	0.1
Antibiotic therapy, n (%)			
β-lactam/macrolide combination	127 (57.7)	103 (59.2)	0.7
Fluoroquinolone	64 (29.1)	30 (17.2)	0.006
β-lactam/quinolone combination	8 (3.6)	18 (10.3)	0.008
β-lactam monotherapy	12 (5.5)	9 (5.2)	0.9
Other*	9 (4.1)	14 (8.0)	0.09

F/M, female/male; COPD, chronic obstructive pulmonary disease; PSI, pneumonia severity index (Fine risk class)
*Other antibiotic regimens.

Table 2 Results of cytokines and markers on days 1 and 3

	Clinical stability		
	⩽3 days	>3 days	
Cytokines	Median (P_{25}–P_{75})	Median (P_{25}–P_{75})	p Value
Day 1			
CRP (mg/dl)	12.2 (5.9–21.6)	17.3 (10.4–28.5)	0.0001
PCT (ng/ml)	0.43 (0.24–1.72)	0.93 (0.34–4.31)	0.0003
TNFα (pg/ml)	27 (16–45)	31 (19–48)	0.1
IL-1 (pg/ml)	21 (7–36)	18 (0–30)	0.08
IL-6 (pg/ml)	63 (25–150)	101 (47–267)	0.0003
IL-10 (pg/ml)	5 (0–17)	10 (3–19)	0.004
IL-8 (pg/ml)	6 (2–14)	6 (2–15)	0.9
Day 3			
CRP (mg/dl)	4.2 (1.8–9.8)	7.0 (2.8–14.2)	0.0003
PCT (ng/ml)	0.33 (0.17–0.60)	0.48 (0.25–1.09)	0.003
TNFα (pg/ml)	26 (14–43)	28 (14–47)	0.4
IL-1 (pg/ml)	13 (4–28)	14 (3–25)	0.8
IL-6 (pg/ml)	24 (7–75)	49 (16–111)	0.003
IL-10 (pg/ml)	4 (0–14)	6 (2–19)	0.03
IL-8 (pg/ml)	7 (2–14)	6 (2–15)	0.9

CRP, C-reactive protein; IL, interleukin; PCT, procalcitonin; TNFα, tumour necrosis factor α.

3 (dependent variable). Independent variables were clinical stability within the first 72 h of treatment, levels of CRP on day 3 and levels of PCT on day 3.

In order to calculate the predictive value of markers (CRP and PCT) together with clinical criteria of stability, the area under the ROC curve (AUC) was calculated from the multivariate logistic regression analyses performed with several combinations. For each regression logistic model the AUC was calculated for absence of severe complications. Statistical comparison of AUCs was conducted according to the Hanley and McNeil method;[14] p values <0.05 were considered significant. For resulting models, sensitivity, specificity and positive and negative predictive values were calculated. Hosmer and Lemeshow goodness-of-fit test was performed for each model.[15]

RESULTS

Patient population

During the study period 394 patients with a mean (SD) age of 66.5 (17.2) years were included. Clinical stability after 72 h of antibiotics was reached by 220 patients (55.8%). Main demographic characteristics, comorbidity and initial severity in the two groups with clinical stability at 72 h or later are shown in table 1. Prescribed initial antimicrobial treatments were: 250 (58.3%) β-lactam (ceftriaxone/cefotaxime or co-amoxi-clavulanate) plus macrolide (clarithromycin or azithromycin), 99 (23.1%) fluoroquinolone (levofloxacin), 29 (6.8%) β-lactam plus quinolone, 24 (5.6%) β-lactam as monotherapy and 27 (6.3%) other regimens. The differences between groups are shown in table 1.

Twenty-four patients (5.6%) died during hospitalisation. Mortality within 30 days was 6.8% (29 patients). After 72 h of treatment, 31 patients (7.2%) developed severe complications: 4 were admitted to the ICU, 8 required mechanical ventilation, 10 suffered from shock and 23 died.

Most frequently found microorganisms were: *Streptococcus pneumoniae* (n = 79, 20%), *Legionella pneumophila* (n = 17, 4.3%), *Staphylococcus aureus* (n = 10, 2.5%), *Haemophilus influenzae* (n = 11, 2.8%), *Pseudomonas aeruginosa* (n = 10, 2.5%), *Escherichia coli* (n = 5, 1.3%), *Mycoplasma pneumoniae* (n = 5, 1.3%) and 27 other microorganisms. Mixed aetiology was found in 24 patients; 14 had *S pneumoniae* together with other microorganisms.

Clinical stability and markers

Univariate analyses

The results of markers CRP and PCT according to clinical stability or not are shown in table 2.

Median levels of CRP, PCT, IL-6 and IL-10 were significantly higher in patients who did not reach clinical stability at day 3 (fig 1). Cut-off points of markers to predict the absence of severe complications were selected with the highest specificity and positive predictive value in order not to underestimate any severe complication. After day 3, 5/103 patients with PCT levels <0.25 ng/ml developed severe complications compared with 22/213 patients with higher PCT levels (p<0.05), and 3/105 patients with CRP levels <3 mg/dl developed severe complications compared with 24/214 patients with higher CRP levels (p<0.05).

Fifteen patients had CRP levels <3 mg/dl and PCT levels <0.25 ng/ml but did not achieve clinical stability by clinical criteria, and two patients (13.3%) had subsequent severe complications (one death and one severe respiratory insufficiency with non-invasive mechanical ventilation).

One hundred and thirty-five patients achieved clinical stability on day 3, but PCT and CRP levels remained high; complications occurred in three patients (2.2%) (one septic shock and two died).

When clinical stability was also included in the prediction, the following results were obtained: clinical stability reached and PCT <0.25 ng/ml: 0/28 patients developed severe complications versus 28/291 who did not achieve clinical stability and had higher PCT levels (p<0.015). Similar findings were reported for CRP levels ⩽3 mg/dl and clinical stability on day 3: 0/30 developed severe complications vs 30/293 patients without stability and higher CRP levels (p<0.012). The diagnostic value for identifying the absence of severe complications is shown in table 3. When both markers are added to the clinical stability criteria, the predictive value did not increase.

Multivariate analyses

Three logistic regression analyses were performed to predict severe complications after 72 h of treatment (dependent variable). The first model included clinical stability and levels of CRP on day 3 as the independent variable, the second model

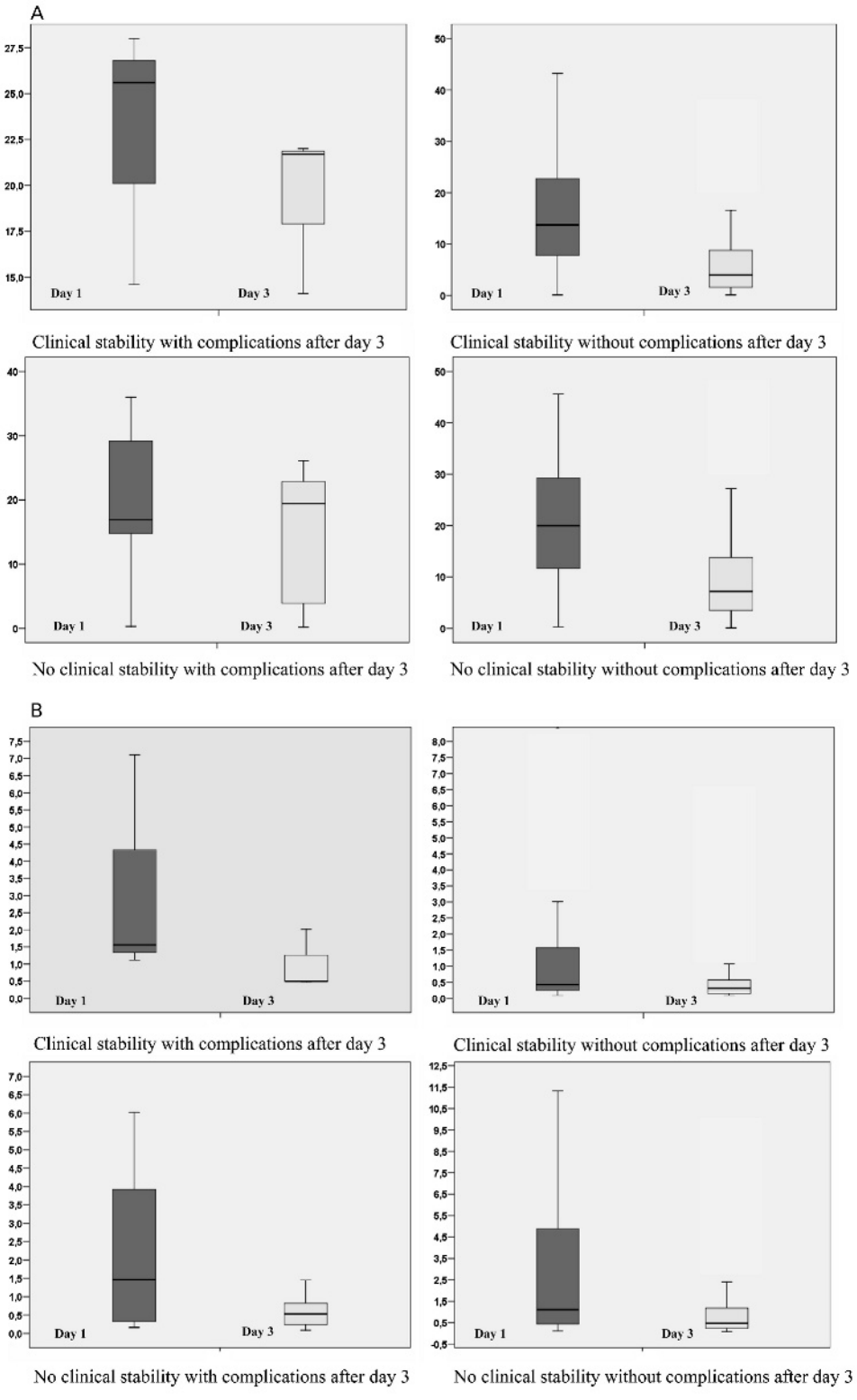

Figure 1 Median levels of (A) C-reactive protein (CRP) and (B) procalcitonin (PCT) stratified by clinical stability with or without severe complications appearing after 72 h.

included clinical stability and levels of PCT, and the third model included clinical stability and levels of CRP and PCT. Clinical stability was a significant independent predictor for the absence of severe complications (0.78 (95% CI 0.71 to 0.86)). CRP was also found to be a significant independent predictor (0.86 (95% CI 0.77 to 0.97)), but PCT was not independently associated (1.17 (95% CI 0.78 to 1.76)).

The AUCs of the different logistic regression models with combinations of markers and clinical stability were calculated. The AUC to predict the absence of severe complications after day 3 using clinical stability was 0.77 (95% CI 0.64 to 0.90); when the CRP value was added, the area increased to 0.84 (95% CI 0.75 to 0.92), p = 0.059; and, when PCT was added, it was 0.77 (95% CI 0.63 to 0.91), p = 0.45.

DISCUSSION

The most important findings of our study are (1) that markers improve safety in predicting the absence of complications with

Table 3 Predictive value of clinical stability criteria and biomarkers on day 3 for the absence of severe complications after 72 h

Clinical criteria and biomarkers	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	OR (95% CI)	LR+	LR−
Clinical stability	58	83	99	9	6.8 (2.0 to 22.4)	3.5 (1.5 to 9.9)	0.5 (0.4 to 0.7)
CRP <3 mg/dl	35	89	97	11	4.2 (1.3 to 13.7)	3.1 (1.2 to 9.1)	0.7 (0.6 to 0.9)
PCT <0.25 ng/ml	34	81	95	10	2.2 (0.8 to 5.9)	1.8 (0.9 to 4.2)	0.8 (0.7 to 1.05)
Clinical stability + CRP <3 mg/dl	19	100	100	10	14.1 (1.4 to 138.8)	11.4 (1.3 to 110.0)	0.8 (0.7 to 0.9)
Clinical stability + PCT <0.25 ng/ml	19	100	100	10	13.4 (1.4 to 131.7)	10.8 (1.3 to 104.0)	0.8 (0.7 to 0.9)
Clinical stability + CRP <3 mg/dl + PCT <0.25 ng/ml	9	100	100	9	5.8 (0.6 to 57.5)	5.3 (0.6 to 51.4)	0.9 (0.8 to 1.1)

CI, confidence interval; CRP, C-reactive protein; LR+, positive likelihood ratio; LR−, negative likelihood ratio; NPV, negative predictive value; OR, odds ratio; PCT, procalcitonin; PPV, positive predictive value.

respect to the clinical criteria of stability; and (2) that a reduction in PCT levels to <0.25 ng/ml and CRP levels to <3 mg/dl together with clinical stability permits identification of patients with a high negative predictive value without subsequent severe complications.

Objective parameters such as these markers to identify clinical stability and to determine that the patient will not develop severe complications would be very useful to clinicians. This information is important to decide on subsequent follow-up, sequential treatment and possible discharge. It is well known that, if a patient is discharged when unstable, the likelihood of death is higher.[16 17] It is also known that the time between reaching clinical stability—mean of 3 days[2 11 17]—and discharge prolongs hospital stay,[18] mainly because of a conservative or protective attitude to the possibility of complications arising after stability has been achieved and the lack of capacity to anticipate them. In fact, a modifiable process of care would be to reduce this time safely for the patient. Although previous studies have shown that one day of in-hospital observation is not necessary after achieving stability and switching antibiotic treatment,[19] some authors reported a non-significant trend towards lower 30-day mortality in a cohort receiving in-hospital observation. This finding, together with studies reporting that a reduction in length of stay was associated with a trend towards higher 30-day mortality, suggests that the clinical benefit of in-hospital observation cannot definitively be ruled out.[20]

Our results show that patients who achieved clinical stability within the first 72 h had significantly lower initial levels of PCT, CRP and cytokines (IL-6 and IL-10). These findings are plausible and support the idea that markers express the degree of systemic inflammation and reflect the response to resolution of the infection. Thus, high levels of markers and cytokines after 72 h of treatment are associated with therapeutic failure[1] and death.[21] Kellum *et al*[21] have shown that the higher the initial levels of cytokines the worse the prognosis, and that the reduction in cytokine levels was faster during the first 3 days.[21 22] Interestingly, persistence of inflammation after 72 h also has implications in medium- to long-term mortality.[23] Yende *et al*[23] showed that high levels of IL-6 (mean 6.0 pg/ml) at discharge and, to a lesser degree, of IL-10 (1.2 pg/ml) can increase the probability of death in the period between discharge and 3 months thereafter.

The capacity of CRP alone to predict severe complications at day 3 reached a diagnostic value similar to clinical criteria, with specificity and positive predictive value similar to the stability clinical criteria. We found that information on the reduction of systemic inflammation was complementary to clinical stability in ruling out subsequent complications. The study by Halm *et al*[2] pointed out that severe complications are unlikely after clinical stability has been achieved, but progressive ageing of the population, an increase in the number of comorbidities and of multiple associated treatments (such as steroids) can interfere with the stability parameters. Our study confirms the high predictive value of the absence of severe complications after reaching stability (3/135 patients (2.2%) with severe complications), but we found that these three patients still had high levels of CRP and PCT. In fact, the AUC for CRP to predict the absence of complications (AUC 0.77–0.84) increases the safety of clinical criteria for predicting complications. To calculate the threshold for the two markers, we selected that with a higher specificity and positive predictive value for the absence of severe complications. Although the addition of CRP or PCT to stability criteria only increased the specificity slightly, it was clinically highly relevant since it increased the safety for predicting the absence of severe complications.

It is also interesting to analyse the progress of patients with clinical instability on day 3 but with levels of biological markers below the established cut-off points. The probability of severe complications was also low (2.9% if the CRP level was <3 mg/dl and 4.9% if the PCT level was <0.25 ng/ml), and lower than if the levels of these markers remained high. Capelastegui *et al*[17] reported that the clinical parameters of instability at discharge had a greater impact on mortality. Of the four parameters analysed (persistence of fever, systolic blood pressure <90 mm Hg, respiratory rate >24 and oxygen saturation below 90%), they found that persistence of fever had a closer relationship with mortality, which may be due to a higher systemic inflammation.

The importance of the reduction in the PCT levels has been used to calculate the duration of antibiotic treatment.[6] These studies show that PCT levels <0.25 ng/ml can be used to indicate suspension of treatment. Nevertheless, to our knowledge, there are no studies analysing the levels of markers together with stability information in CAP. The use of markers as an expression of inflammation is complementary to clinical parameters, alerting the clinician if they remain high—even if clinical stability is reached—and reducing the level of alert if they are reduced. The economic implications of early and safe discharge are enormous.

In conclusion, our results have shown that both clinical criteria of stability and reduction of biomarker levels after 72 h of treatment have a high negative predictive value for ruling out subsequent severe complications. The addition of the biological information provided by CRP and PCT levels to clinical criteria of stability improved the safety of that prediction. This

information, if confirmed in other studies, would provide practical and useful information for safe early discharge in hospitalised patients with CAP.

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