Biomarkers improve mortality prediction by prognostic scales in community-acquired pneumonia.

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Key words: procalcitonin, c reactive protein, interleukin, prognosis
ABSTRACT.

**Background**: Prognostic scales provide a useful tool to predict mortality in community-acquired pneumonia (CAP). However, the inflammatory response of the host, crucial in resolution and outcome, is not included in the prognostic scales.

**Methods**: We aimed to investigate whether information about the initial inflammatory cytokine profile and markers increases the accuracy of prognostic scales to predict 30-days mortality. To this aim a prospective cohort study in two tertiary care hospitals was designed. Procalcitonin (PCT), C-reactive protein (CRP), and the systemic cytokines tumor necrosis factor α (TNFα), interleukins IL-6, IL-8 and IL-10 were measured at admission. Initial severity was assessed by PSI (pneumonia severity index), CURB-65 and CRB65 scales. 453 hospitalized CAP patients were included.

**Results**: The 36 patients who died (7.8%) had significantly increased levels of IL-6, IL-8, PCT and CRP. In regression logistic analyses, high levels of CRP and IL-6 showed independent predictive value for predicting 30-days mortality, after adjustment for prognostic scales. Adding CRP to PSI significantly increased the area under the ROC curve (AUC) from 0.80 to 0.85, that of CURB-65 from 0.82 to 0.85 and that of CRB65 from 0.79 to 0.85. Adding IL-6 or PCT values to CRP did not significantly increase AUC of any scale. When using simultaneously both scales and CRP the AUC was 0.88.

**Conclusions**: Adding CRP levels to PSI, CURB-65 and CRB-65 scales improves the 30-days mortality prediction. The highest predictive value is reached with a combination of two both scales and CRP. Further validation of that improvement is needed.

**Word count**: 249
INTRODUCTION

Community-acquired pneumonia (CAP) continues to be a worldwide health problem. Its annual incidence is 3-5‰ in the adult population and mortality reaches 5-15% in admitted patients, thus representing the first cause of death by infectious disease [1-3], as reported by the ERS (European Respiratory Society) [2] and found in data from the United States [4,5]. This justifies the interest to identify prognostic factors and to develop tools able to predict mortality. The publication during the 90’s of the Fine risk scale, the Pneumonia severity Index (PSI)[6], to predict mortality in CAP represented a significant advance, as also did the more recent CURB-65 scale and its simplified version CRB-65[7]. Both scales have been validated[8,9], but they have some limitations and they are believed to best evaluate opposite severity spectrums. Both scales calculate at diagnosis the probability of death but they do not assess the inflammatory response of host, which is currently considered a key aspect in the prognosis of the patient [10].

A new approach is to evaluate biological parameters, as an expression of the host inflammatory response against the microorganism, in order to identify the defense capacity of the patient and to individualize the prognosis. In that response, the host produces an amount of proinflammatory and anti-inflammatory cytokines that depends on genetic polymorphisms, the microorganism and the initial severity of the disease[10]. Although these mediators have a beneficial effect, an excessive cytokine release has been associated with deleterious effects such as hypotension, myocardial dysfunction, hypoperfusion of vital organs, lactic acidosis and higher mortality[10-12]. Biological markers of infection and inflammation have raised much interest because of their ability to reflect the inflammatory response of the host faster and more feasibly. Previous studies with C-reactive protein (CRP), procalcitonin (PCT) and more recently pro-adrenomedullin[13] have showed their correlation with initial severity and with poor outcome.

Our hypothesis is that the inclusion of biological markers, as expression of the systemic inflammatory response, would yield additional information and would be able to improve the 30-days mortality prediction of the two most used prognostic scales, the pneumonia severity index (PSI) and the CURB-65/CRB-65 scales, in patients hospitalized due to CAP. Therefore we analyzed the diagnostic value of the scales to predict mortality adding the information of the cytokines IL-6, IL-8, IL-10. TNF-α, and the markers CRP and PCT.

PATIENTS AND METHODS

A prospective longitudinal study was performed in patients with CAP consecutively hospitalized in two hospitals. The inclusion criteria were a new radiographic infiltrate and at least two compatible clinical symptoms. Exclusion criteria were admission within the previous 15 days, immunosuppressive treatment and/or steroids (>15 mg/day), leucopenia < 1,000/mm³ or neutropenia < 500/mm³ (except if attributable to CAP) and patients with DNR-orders. The study was approved by the two Ethics Committees and the patients signed an informed consent.

Data collection:

Data were collected about age, gender, smoking and alcohol habits (>80 gr/day), co-morbid diseases such as chronic obstructive pulmonary disease (COPD), and cardiac, liver, renal or central nervous system (CNS) disorders. Recorded clinical signs and symptoms were: cough, expectoration, pleuritic chest pain, dyspnea, acute confusion, temperature, respiratory and heart rates, systolic and diastolic blood pressure and the presence of rales. The following analytical data were recorded: leukocyte count, sodium,
potassium, serum creatinine, ALT/AST and arterial blood gas analysis. The PSI[6], CURB-65 and CRB65 were also recorded[14].

Surviving patients underwent follow-up radiological and serologic study after 30 days. The endpoint variable was death within 30 days of admission.

Cytokines, PCT and CRP determinations.

Blood samples were drawn in the first day. Blood was centrifuged, coded and frozen at –80 °C until subsequent analyses. The determination of IL-6, IL-8, IL-10 and TNF-α was performed with a commercial enzymoimmunoassay technique (BioSource, Nivelles, Belgium). The limits of detection were 3 pg/mL for TNF-α, 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, Italia) with a detection limit of 0.3 ng/mL. CRP was measured using an immunoturbidimetric method using a commercially available test (Bayer Diagnostics) with an Advia 2400.

Statistical analysis

Statistical analysis was performed with the SPSS 15.0 software. The chi-square test was used for categorical variables, and the Student’s t or Mann-Whitney U tests for continuous variables. Correlation was analyzed using the Spearman’s rho correlation analysis.

Multivariable logistic regression was performed to predict 30-days mortality (dependent variable); independent variables were initial severity, cytokines and PSI scale was stratified as follows: classes I-II, III, IV and V. CURB-65 was as 0-1, 2, 3, 4-5. CRB65 was as 0-1, 2, 3-5.

In order to calculate the diagnostic value of markers, cytokines, PSI and/or CURB-65/CRB-65 scales to predict 30-days mortality, multivariable logistic regression analyses were performed with several combinations. First, the logistic regression models included CRP and PCT as independent variables, and were adjusted either for PSI, for the CURB-65 and for CRB-65 scale. Next, cytokines were added to each model as independent variables and multivariable analyses were repeated. For each regression logistic model, the area under the ROC curve (AUC) was calculated for 30-days mortality prediction. Statistical comparison of AUCs was conducted according to the Hanley and McNeil method[15]; 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[16].

RESULTS

Patient population

During the study period 480 patients were eligible; the study group comprised 453 patients (419 of them with complete results of all cytokines and markers) with a mean age of 67.3±17.1 years. Mortality within 30 days was 7.9% (36 patients); 31 of them died during hospitalization (in-mortality 6.8%). The main demographic characteristics, comorbidity and initial severity measured by the two prognostic scales (PSI and CURB-65) are shown in Table 1.

### Table 1. Characteristics and Initial Severity of the Groups with and without Mortality

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>30-days mortality</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes n= 36 (7.9%)</td>
<td>No n= 417 (92.1%)</td>
</tr>
</tbody>
</table>

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Patients who died were older, had more neurological diseases and higher initial severity, more patients belonged to PSI class V and CURB-65 class >3. Most frequently found microorganisms were: 81 S. pneumoniae (18%), 17 Legionella pneumophila (4%), 12 S. aureus (3%), 12 H. influenzae, 11 Pseudomonas aeruginosa, 6 Escherichia coli (1%), 5 Mycoplasma pneumoniae and 28 other microorganisms. We found mixed etiology in 26 patients: 15 of them had S. pneumoniae together with other microorganisms.  

**Initial severity, systemic cytokines and markers.**

Results of cytokines and markers according to the prognostic scales are shown in Table 2a and 2b.
TABLE 2a. MEDIAN (P25-P75) OF CYTOKINES AND MARKERS ACCORDING TO INITIAL SEVERITY IN PSI.

<table>
<thead>
<tr>
<th>PSI</th>
<th>I-II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP mg/dL</td>
<td>15.9 (7.8-24.3)</td>
<td>13.6 (5.8-20.4)</td>
<td>15.5 (8.2-26.2)</td>
<td>18.7 (8.7-28.3)</td>
<td>0.2</td>
</tr>
<tr>
<td>PCT ng/mL</td>
<td>0.43 (0.2-1.5)</td>
<td>0.43 (0.25-1.6)</td>
<td>0.74 (0.3-2.8)</td>
<td>2.2 (0.8-11.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>IL-6 pg/mL</td>
<td>72 (26-202)</td>
<td>79 (34-208)</td>
<td>66 (28-185)</td>
<td>134 (41-383)</td>
<td>0.08</td>
</tr>
<tr>
<td>IL-8 pg/mL</td>
<td>6 (0-17)</td>
<td>5 (2-11)</td>
<td>5 (1-16)</td>
<td>14 (4-32)</td>
<td>0.01</td>
</tr>
<tr>
<td>IL-10 pg/mL</td>
<td>5 (1-15)</td>
<td>8 (2-20)</td>
<td>9 (2-23)</td>
<td>10 (0-36)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

TABLE 2B. MEDIAN (P25-P75) OF CYTOKINES AND MARKERS ACCORDING TO CURB-65 AND CRB-65.

<table>
<thead>
<tr>
<th>CURB-65</th>
<th>CRB-65</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>2</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>14.9 (7.1-23.4)</td>
</tr>
<tr>
<td>PCT (ng/mL)</td>
<td>0.41 (0.24-1.4)</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>71 (34-179)</td>
</tr>
<tr>
<td>IL-8 (pg/mL)</td>
<td>6 (1-14)</td>
</tr>
<tr>
<td>IL-10 (pg/mL)</td>
<td>10 (5-17)</td>
</tr>
</tbody>
</table>

The medians were significantly higher in more severe disease for PCT and IL-8 in both scales. We didn’t find any significant difference concerning prior treatment before admission or not for any marker or cytokine.

A correlation analysis of cytokines and markers with initial severity showed that the PCT had the highest positive correlation with PSI (rho 0.27, p<0.0001), CURB-65 (rho 0.29, p<0.0001) and CRB-65 (rho:0.26, p<0.0001) scales. IL-8 also showed a low positive but significant correlation with CURB-65 (rho 0.11, p<0.02) and IL-10 with PSI (rho 0.12 p<0.01), CURB-65 (rho 0.11 p<0.02) and CRB-65 (rho:0.1, p<0.001) scales. The correlation of the cytokines with CRP and PCT was studied. A positive correlation was found for CRP with IL-6 (rho 0.55, p<0.0001) and with IL-8 (rho 0.14, p<0.001). Furthermore, a positive correlation was also found for PCT with IL-6 (rho 0.40, p<0.0001), but not with IL-8. Correlation between both markers -CRP and PCT- was also significant (rho 0.48, p<0.0001).

**Diagnostic value of markers and cytokines to predict 30-days mortality.**

The results of cytokines and markers in the groups of patients who died and of those who survived are displayed in Table 3. Significantly higher levels of IL-6 IL-8, CRP and PCT were found in patients who died within 30 days.
TABLE 3. MEDIANS (P25-P75) OF CYTOKINES AND MARKERS IN GROUPS WITH AND WITHOUT MORTALITY

<table>
<thead>
<tr>
<th>Cytokine day 1</th>
<th>Mortality</th>
<th>Yes</th>
<th>No</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP, mg/dL</td>
<td>21.9 (16.0-32.2)</td>
<td>14.4 (7.3-23.5)</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>PCT, ng/mL</td>
<td>1.8 (0.63-13.07)</td>
<td>0.58 (0.27-2.38)</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>TNF-α, pg/mL</td>
<td>44 (17-79)</td>
<td>29 (17-46)</td>
<td>0.069</td>
<td></td>
</tr>
<tr>
<td>IL-6, pg/mL</td>
<td>191 (75-982)</td>
<td>73 (29-197)</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>IL-8, pg/mL</td>
<td>36 (10-65)</td>
<td>6 (2-14)</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>IL-10, pg/mL</td>
<td>10 (0-65)</td>
<td>7 (1-19)</td>
<td>0.25</td>
<td></td>
</tr>
</tbody>
</table>

Definition of abbreviations: CRP= C-reactive protein; PCT= procalcitonin.

The diagnostic value of markers, cytokines and prognostic scales to predict 30-days mortality was assessed with areas under the ROC curve, with the following results: CRP 0.68 (95%CI 0.59-0.76), PCT 0.66 (0.56-0.76), IL-6 0.68 (0.58-0.78), IL-8 0.76 (0.67-0.86), IL-10 0.55 (0.44-0.68), TNF-α 0.59 (0.47-0.71).

The multivariable study to predict mortality when all cytokines and markers were included found that, after adjustment for PSI and CURB-65, the model selected CPR and IL-6 as independent predictive variables. The best cut-off point for CRP, using the highest values of sensitivity and specificity after constructing a ROC curve, was 25 mg/dL. Ninety nine patients had levels equal to or higher than this level: 38 (38.4%) developed treatment failure versus 42 (13.1%) of 320 with CRP<25, 13 presented shock (14% versus 17/316 or 5.4%), 18 required ICU admission (18.2% versus 27/320 or 8.4%), and 7 required mechanical ventilation (7.1% versus 12/320 or 3.8%). The results of mortality in each prognostic scale depending on the threshold of CRP are depicted in Table 4.

TABLE 4. MORTALITY ACCORDING TO INITIAL SEVERITY, AND LEVEL OF CRP IN MG/DL.

<table>
<thead>
<tr>
<th>CRB-65</th>
<th>CRP &lt;25</th>
<th>CRP ≥25</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>3/200 (1.5%)</td>
<td>2/53 (3.77%)</td>
</tr>
<tr>
<td>2</td>
<td>10/90 (11.1%)</td>
<td>3/24 (12.5%)</td>
</tr>
<tr>
<td>≥3</td>
<td>8/30 (26.6%)</td>
<td>9/22 (40.9%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CURB-65</th>
<th>CRP &lt;25</th>
<th>CRP ≥25</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>1/148 (0.7%)</td>
<td>1/41 (2.4%)</td>
</tr>
<tr>
<td>2</td>
<td>4/92 (4.3%)</td>
<td>2/26 (7.7%)</td>
</tr>
<tr>
<td>≥3</td>
<td>16/80 (20%)</td>
<td>11/32 (34.4%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PSI</th>
<th>CRP &lt;25</th>
<th>CRP ≥25</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-II</td>
<td>0/86</td>
<td>0/25</td>
</tr>
<tr>
<td>III</td>
<td>2/76 (2.6%)</td>
<td>0/13</td>
</tr>
<tr>
<td>IV</td>
<td>8/114 (7%)</td>
<td>6/39 (15.4%)</td>
</tr>
<tr>
<td>V</td>
<td>11/44 (25%)</td>
<td>8/22 (36.4%)</td>
</tr>
</tbody>
</table>

deaths / total numbers in each group (%)

Deaths / total numbers in each group (%)

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The AUCs of the different logistic regression models with combinations of markers and cytokines joined to any or both prognostic scales were calculated (Table 5).

### TABLE 5. AREAS UNDER THE ROC CURVE (AUC) OF THE DIFFERENT MODELS TO PREDICT 30-DAYS MORTALITY.

<table>
<thead>
<tr>
<th></th>
<th>AUC</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSI</td>
<td>0.81</td>
<td>0.75-0.87</td>
</tr>
<tr>
<td>PSI + CRP *</td>
<td>0.85</td>
<td>0.80-0.91</td>
</tr>
<tr>
<td>PSI + PCT</td>
<td>0.83</td>
<td>0.77-0.89</td>
</tr>
<tr>
<td>PSI + CRP + PCT*</td>
<td>0.85</td>
<td>0.79-0.91</td>
</tr>
<tr>
<td>PSI + CRP + IL-6 *</td>
<td>0.86</td>
<td>0.80-0.92</td>
</tr>
<tr>
<td>PSI + CRP + IL-8 *</td>
<td>0.87</td>
<td>0.82-0.93</td>
</tr>
<tr>
<td>CRB-65</td>
<td>0.79</td>
<td>0.72-0.87</td>
</tr>
<tr>
<td>CRB-65 + CRP**</td>
<td>0.85</td>
<td>0.79-0.90</td>
</tr>
<tr>
<td>CRB-65 + PCT</td>
<td>0.83</td>
<td>0.76-0.89</td>
</tr>
<tr>
<td>CRB-65 + CRP + PCT**</td>
<td>0.86</td>
<td>0.80-0.92</td>
</tr>
<tr>
<td>CRB-65 + CRP + IL-6**</td>
<td>0.86</td>
<td>0.80-0.92</td>
</tr>
<tr>
<td>CRB-65 + CRP + IL-8**</td>
<td>0.88</td>
<td>0.81-0.93</td>
</tr>
<tr>
<td>CURB-65</td>
<td>0.82</td>
<td>0.76-0.89</td>
</tr>
<tr>
<td>CURB-65 + CRP †</td>
<td>0.86</td>
<td>0.81-0.92</td>
</tr>
<tr>
<td>CURB-65 + PCT</td>
<td>0.84</td>
<td>0.77-0.90</td>
</tr>
<tr>
<td>CURB-65 + CRP + PCT †</td>
<td>0.86</td>
<td>0.79-0.92</td>
</tr>
<tr>
<td>CURB-65 + CRP + IL-6†</td>
<td>0.87</td>
<td>0.82-0.92</td>
</tr>
<tr>
<td>CURB-65 + CRP + IL-8 †</td>
<td>0.88</td>
<td>0.83-0.93</td>
</tr>
<tr>
<td>PSI + CRB-65 + CRP *†</td>
<td>0.87</td>
<td>0.81-0.92</td>
</tr>
<tr>
<td>PSI + CRB-65 + CRP*IL-6 *†</td>
<td>0.88</td>
<td>0.82-0.93</td>
</tr>
<tr>
<td>PSI + CURB-65 + CRP *†</td>
<td>0.88</td>
<td>0.83-0.93</td>
</tr>
<tr>
<td>PSI + CURB-65 + CRP + IL-6*†</td>
<td>0.88</td>
<td>0.83-0.94</td>
</tr>
</tbody>
</table>

* p<0.05 for comparison of AUCs with that of PSI
† p<0.05 for comparison of AUCs with that of CURB-65
** p<0.05 for comparison of AUCs with that of CRB-65

The AUC to predict 30-days mortality significantly increases when the CRP value is added both to the PSI, to the CURB-65 and CRB-65 scales. There were increases when IL-6 or IL-8 were further included (0.86 and 0.87 respectively), but they were not significant when compared to the combination of CRP alone with the scales. The best AUC is reached with the PSI together with CURB-65 and CRP 0.88. The diagnostic value of simultaneously using both prognostic scales and CRP with a cut-off point of 25 mg/mL reaches a sensitivity of 0.77, a specificity of 0.78, a positive predictive value of 0.24 and a negative predictive value of 0.97.

The Chi-square goodness-of-fit analysis demonstrated the adequacy of the models (p > 0.05).
DISCUSSION

The most important findings of our study are that the initial value of CRP increases the 30-day mortality prediction by the PSI (AUC from 0.80 to 0.85), the CURB-65 scale (AUC from 0.82 to 0.85) and by the CRB-65 (AUC from 0.79 to 0.85). PCT improves the AUC although without reaching statistical significance. The diagnostic value of CRP and both scales together is the highest, with an AUC of 0.88. Adding the information of cytokines, IL-6 and IL-8, does not significantly increase the predictive value, thus in clinical practice they can be substituted, by CRP.

Mortality by CAP is related to the initial severity evaluated with the prognostic scales, however, these have some limitations: PSI identifies low probability of death better, underestimating risk in young adults, whereas CURB-65 identifies high probability better but does not adequately evaluate patient comorbidity [17]. Niederman [17] has proposed to combine the information of both scales for the assessment of severity and admission decision. In both cases, the scales do not incorporate information of response of the host against infection, which is a key point to alert clinicians as to the possible development of a more severe evolution and/or complications.

An important issue is if the cytokine profile and markers are merely a reflection of initial severity, that is, they yield redundant information or if they provide additional information about host ability to respond against infection[18]. In fact, there have been reports of a positive correlation of severity with IL-6, IL-8 and PCT levels, all three of which we have confirmed. In contrast, CRP did not correlate with PSI, CURB-65 or CRB-65, as reported by other authors [13]. Moreover, despite the positive correlation between prognostic scales and cytokines and PCT, it was unsatisfactory, suggesting that information provided by them is not identical and might offer complementary data. Thus, higher levels of cytokines [19,20] and CRP have been demonstrated in patients who subsequently develop shock or severe respiratory failure even with adequate antimicrobial treatment[18]. In a very interesting paper, Kruger et al, were able to identify, for the same level of severity in CURB-65, patients with higher risk of mortality if PCT was>0.228 [21]. Christ-Crain et al [13] also reported that levels of PCT and pro-adrenomedullin together with PSI improved the AUC for mortality prediction.

In our study we confirm that the initial values of proinflammatory cytokines IL-6 and IL-8 and CRP and PCT were significantly higher in patients with 30-day mortality, similar to prior findings[18,19,22-24]. Furthermore, after stratifying patients according to CRP levels and the three scales, the mortality increased in those with higher levels both in low and high initial risk of mortality. Multivariable analysis corroborated that, after adjusting for the prognostic scales, CRP and IL-6 have independent predictive value. That is, values of CRP above 25mg/dL double the probability of death previously computed in the same class of initial risk. It is worth mentioning that with CRP and both scales together, a very high negative predictive value is reached (97%), despite its lower positive predictive value. Chalmers et al [25] also recently reported that low admission CRP levels were associated with negative predictive value for 30-day mortality, mechanical ventilation, inotropic support and complicated pneumonia. Remarkably, PCT did not significantly improve the prediction of mortality after adjustment for PSI or CURB-65, although Christ-Crain et al[13] reported a slight increase.

The diagnostic value for 30-day mortality prediction was assessed with the estimation of AUCs obtained with logistic regression models. Although the most explicative mathematic model includes a cytokine (IL-6 or IL-8) and a marker (CRP), our goal was to find a simpler model with only one marker for easier application in
clinical practice. With simpler models with only one marker and one scale, significant improvement was also obtained in the AUCs. Our findings show that CRP significantly improved the diagnostic value of both PSI and the CURB-65 /CRB-65 scales, with a similar gain. Nevertheless, if PCT was included, we found a trend to increase without reaching statistical significance (from 0.80 to 0.82 for PSI, 0.81 to 0.84 for CURB65 and 0.79 to 0.83 for CRB-65). A slight increase in the AUC was obtained by simultaneously using both scales and CRP (0.88). The further inclusion of a cytokine to this model did not yield a significant diagnostic improvement. Diagnostic values with cytokines and diagnostic scales are not significantly higher than the values reached with markers, as expected, since CRP and PCT release is increased by bacterial products, toxins, cytokines and IL-6 [26].

One limitation of our study is that outpatients with CAP were not included therefore our results cannot be extrapolated to this population.

In conclusion, the incorporation of the biologic markers, PCT and specially CRP, to the prognostic scales of PSI and CURB-65 might improve their mortality prediction value, to a similar degree for both scales. Measurement of proinflammatory cytokines yields information comparable to that of biologic markers. Markers could be used to improve the mortality prediction of the prognosis, based on the inflammatory response of each patient. Further studies are needed to corroborate the additive value of biological markers.
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