ROLE OF SOME BIOMARKERS IN DETERMINING THE RISK OF MORTALITY OF HOSPITALIZED PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA

Darina Miteva¹, Yordan Radkov¹, Liliya Ivanova², Vanya Kostadinova¹, Trifon Chervenkov³

¹Department of Pulmonology and Allergology, ²Department of Microbiology and Virology,

³Department of Medical Genetics, Faculty of Medicine,

Medical University of Varna, Bulgaria

ABSTRACT

INTRODUCTION: Various biomarkers are used to determine the severity and risk of mortality in community-acquired pneumonia (CAP). The aim of this article is to evaluate the prognostic value for in-hospital mortality of leukocyte count (Leuk), C-reactive protein (CRP), procalcitonin (PCT), and mid-regional proadrenomedullin (MR-proADM) in CAP patients.

MATERIALS AND METHODS: This was a prospective study including a total of 92 CAP patients hospitalized in the Clinic of Pneumology and Phthisiatry at St. Marina University Hospital of Varna. Biomarkers were determined at hospitalization, Leuk - by automated methodology, CRP - by latex-enhanced immunoturbidimetric method, and both MR-proADM and PCT - by standard ELISA. CAP severity was estimated by Pneumonia Severity Index (PSI) and CURB-65.

RESULTS: The patients were at a mean age of 59.2 ± 16.8 years, 68.5% were men. In-hospital mortality was 7.6%. The optimal cut-off value of MR-proADM for in-hospital mortality was 0.88 ng/mL (sensitivity 85.7% and specificity 85.8%). The positive predictive value was 33.3% and the negative predictive value was 98.6%. The optimal cut-off value of PCT was 1.84 ng/mL (sensitivity 71.4% and specificity 81.1%). The positive predictive value was 23.8% and the negative predictive value was 97.1%. Cut-off values for CRP and Leuk could not be established. By performing ROC curves, MR-proADM, PSI, PCT and CURB-65 were good predictors for in-hospital mortality (AUC 0.91, 0.90, 0.89, and 0.86, respectively).

CONCLUSION: MR-proADM and PCT are promising markers in predicting CAP prognosis. Their predictive value for mortality is similar to that of PSI and CURB-65. CRP and Leuk cannot serve as predictors. *Scr Sci Med.* 2017;49(4):58-63

Keywords: community-acquired pneumonia, mid-regional proadrenomedullin, procalcitonin, C-reactive protein, mortality

Address for correspondence:

Darina Miteva, MD
Department of Pulmonology and Allergology
Faculty of Medicine
Medical University of Varna
55 M. Drinov St
Varna 9002
e-mail: dari.miteva@abv.bg

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INTRODUCTION

Biomarkers are quick and objective indicators, therefore their use for the assessment of severity and risk of mortality in community-acquired pneumonia (CAP) is very attractive. Some of them, like leukocyte count (Leuk), have been used for a long time, with leukopenia being a stronger predictor. Thrombocytopenia below $100 \times 10^9/L$ is also associated with an increased risk of mortality and is included in the

IDS/ATS criteria. The C-reactive protein (CRP) is another routinely used marker in CAP diagnosis and monitoring. However, according to the majority of authors, its correlation with the severity scales is weak and its use as a mortality predictor is limited (1,2). Therefore, more reliable predictive markers are being researched. Procalcitonin (PCT), widely used to determine the severity and prognosis of sepsis, has recently been applied to determine the prognosis of other infectious diseases, including CAP. It is a more specific marker for bacterial infection than CRP. Its advantage lies in its ability to distinguish between viral and bacterial infections, thus it can serve as an indicator of the need and duration of antibiotic therapy and can reduce the antibiotic overuse (3-5). However, PCT is more a diagnostic than a predictive marker. Its predictive value for severity and mortality is moderate (6).

Therefore, the search for a better prognostic marker continues and mid-regional proadrenomedullin (MR-proADM) seems to be more promising. Similar to procalcitonin, adrenomedullin belongs to CALC-1-gene family. It is a peptide consisting of 52 amino acids, mainly produced by cardiovascular tissue, but also by the adrenal medulla, lungs, kidneys and neurons. It is one of the most potent endogenous vasodilators. Its levels rise in the syndrome of systemic inflammatory response due not only to infections, but also to burns, trauma, traumatic shock, and pancreatitis (7). Its direct measurement is difficult and for practical purposes a part of the molecule of its precursor known as MR-proADM is used. It has no biologically active properties, however, based on its levels, adrenomedullin levels can be calculated. The correlation between MR-proADM and the severity scales is better than that of PCT, moreover, its addition to these scales can improve their predictive value (8-10). A modified CURB-65-A scale for better identification of high-risk patients has even been introduced (11).

The aim of this article is to evaluate the prognostic value for in-hospital mortality of Leuk, CRP, PCT, and MR-proADM in CAP patients.

MATERIALS AND METHODS

The study was approved by the institutional Ethics Committee and informed consent was obtained. It was a prospective study including a to-

tal of 92 CAP patients hospitalized in the Clinic of Pneumology and Phthisiatry at St. Marina University Hospital of Varna. CAP patients over 18 years of age with radiological confirmation of the diagnosis were included in the study. Patients with CAP associated with lung carcinoma or pulmonary embolism and immunocompromised patients were excluded. Biomarkers were determined at hospitalization, Leuk - by automated methodology, CRP - by latex-enhanced immuno-turbidimetric method, and both MR-proADM and PCT - by standard ELISA. CAP severity was estimated by Pneumonia Severity Index (PSI) and CURB-65.

SPSS v.20 statistical software was used for data analyses. Comparative analysis (Student *t*-test and χ^2) was used. Quantitative variables were reported as mean and standard deviation (mean $\pm$ SD) and the qualitative variables were reported as a number and a relative share (%). $P < 0.05$ was considered statistically significant. For determining cut-off values, ROC curves were constructed. To evaluate the impact of the biomarkers and scales on the mortality, uni- and multivariate regression analysis and ROC analysis were used.

RESULTS

The patients were at a mean age of 59.2 ± 16.8 years, 68.5% were men. Seven patients (7.6%) died in the hospital. Twenty-two patients (23.9%) were treated in the Intensive Care Unit. The characteristics of survived and deceased patients and the mean values of the biomarkers are shown in Table 1.

We did not find any significant difference in the age of survived and deceased patients. The non-survivors had a significantly higher PSI score and fell significantly more often into the high-risk groups according to PSI and CURB-65. There were no deceased patients in the low-risk groups CURB-65=0-1 and PSI=1-3. In CURB-65=2 (intermediate-risk group), 11.8% of patients died, and in the high-risk groups CURB-65 $\geq$ 3 and PSI=4-5, the mortality rate was 29.4% and 23.3%, respectively. MR-proADM, PCT and CRP were significantly higher in non-survivors compared to survivors (0.918 ± 0.045 ng/mL vs. 0.397 ± 0.269 ng/mL, $p < 0.001$; 2.14 ± 0.60 ng/mL vs. 1.12 ± 0.68 ng/mL, $p < 0.001$ and 215.12 ± 96.39 mg/L vs. 175.74 ± 221.5 mg/L, $p < 0.05$). There was no significant difference in Leuk.

Table 1. Characteristics of the studied group

Characteristic	Survivors	Non-survivors	p-value
Age (years)	58.4±16.6	69.1±17.8	0.10 (NS)
Mean PSI score	81.76±31.19	153.43±33.2	<0.001
PSI = 1-3	62 /100%	-/ 0%	<0.001
PSI = 4-5	23 /76.6%	7 /23.3%	
CURB-65=0-1	56/ 100%	-/ 0%	<0.001
CURB-65=2	15 / 88.2%	2 /11.8%	
CURB-65≥3	12 / 70.6%	5 /29.4%	
Leuk x10 ⁹ /L	11.33±5.66	11.34±7.76	>0.05 (NS)
CRP mg/L	175.74±221.5	215.12±96.39	<0.05
PCT ng/ml	1.12±0.68	2.14±0.60	<0.001
MR-proADM ng/ml	0.397±0.269	0.918±0.045	<0.001

By building ROC curves, we established cut-off values of the biomarkers for in-hospital mortality. For MR-proADM, we determined a cut-off value of 0.88 ng/mL (sensitivity 85.7% and specificity 85.8%). The positive likelihood ratio was 6.14, and the negative likelihood ratio was 0.16. The positive predictive value was 33.3% and the negative predictive value was 98.6%. For PCT, we determined a cut-off value of 1.84 ng/mL (sensitivity 71.4% and specificity 81.1%). The positive likelihood ratio was 3.73, and the negative likelihood ratio was 0.36. The positive predictive value was 23.8%, and the negative predictive value was 97.1%. For CRP and Leuk, cut-off values could not be estimated.

We build ROC to compare the predictive value for mortality of PSI, CURB-65 and the biomarkers (Table 2). The highest area under the curve (AUC) showed MR-proADM followed by PSI, PCT and

CURB-65, as the AUCs for these four indicators were similar. CRP and Leuk were not significant predictors of mortality.

These results were also confirmed by a univariate logistic regression analysis of mortality. CRP and Leuk again were not significant predictors, whereas the severity scales and the other two biomarkers confirmed their role as significant predictors of mortality. The results are presented in Table 3.

In a multivariate 'stepwise' regression analysis, only MR-proADM (beta 0.42, p<0.001) and PSI (beta 0.39, p=0.001) remained significant mortality predictors.

DISCUSSION

Comparing the groups of deceased and survived patients, we found a higher age for the deceased, but the difference did not reach significance, probably, due to the relatively small number of our sample. Age is a predictor of mortality in most studies and

Table 2. Predictive value for mortality of the scales and biomarkers - ROC analysis

Indicator	AUC	p-value
PSI	0.90 (0.81-0.98)	0.001
CURB-65	0.86 (0.75-0.97)	0.004
MR-proADM	0.91 (0.84-0.98)	0.001
PCT	0.89 (0.79-0.99)	0.002
CRP	0.61 (0.38-0.83)	>0.05 (NS)
Leuk	0.42 (0.15-0.69)	>0.05 (NS)

Table 3. Predictive value for mortality of the scales and biomarkers. Univariate logistic regression analysis

Indicator	beta- coefficient	p-value
PSI	0.54	<0.001
CURB-65	0.38	0.001
MR-proADM	0.93	<0.001
PCT	0.49	<0.05
CRP	0.04	>0.05 (NS)
Leuk	0.03	>0.05 (NS)

is included in the major prognostic scales CURB-65 and PSI (12,13). These scales are the main prognostic tools and other predictors such as biomarkers are compared to them. In our study, all non-survivors fell into high-risk groups according to PSI=4-5. According to CURB-65, all deceased fell into intermittent and high-risk groups. The mortality rate in the severity groups corresponded to that one in the original documents, whereas in the high-risk groups, this slightly exceeded it, e.g. CURB-65 predicted 22% mortality in the groups ≥ 3 (12) and we found a mortality rate of 29.4%.

We established significantly higher values of CRP, PCT and MR-proADM in non-survivors compared to survivors. Other authors also reported similar results (10,14-19). McCuskey *et al.* reported significantly higher PCT values in patients with bacteremia and in ICU patients, but not in non-survivors (20). In our study, only the Leuk did not show a significant difference between survivors and non-survivors. Although CRP was significantly higher in the deceased patients, it failed (along with the Leuk) as a significant predictor of mortality. Similar results were also reported by other authors. Thiem *et al.* did not establish any correlation between initial CRP and Leuk, on the one hand, and mortality, on the other hand, in a cohort of adult patients over 65 years of age (2). In a systematic review, Engel *et al.* did not report poor outcome of pneumonia in patients with high CRP, too (1). In contrast to CRP, most authors found a better predictive value for PCT and especially for MR-proADM, as did our results. In a meta-analysis, elevated PCT was established as a risk factor for mortality with RR 4.38 (2.98-6.43; 95% CI) (21). A higher AUC for MR-proADM than for PCT in predicting 30-day mortality (0.76 versus 0.65; $p < 0.001$) was reported (9). Even higher AUC of MR-proADM for 30-day mortality of 0.892 ($p < 0.001$) was reported (22). By building ROC curves, Schuetz *et al.* also found out that MR-proADM had a similar predictive value for mortality with PSI which was better than that of CURB-65 (23). Bello *et al.* found better correlation coefficients of MR-proADM with the severity scales compared to other biomarkers and emphasized its advantages as a prognostic marker (8).

In our study, we found that the AUC of the two biomarkers MR-proADM and PCT and, subsequently, their prognostic value for mortality was similar to

that of the major scales. We determined cut-off values for mortality of the studied biomarkers. For MR-proADM, we estimated a cut-off value of 0.88 ng/mL (sensitivity 85.7% and specificity 85.8%). For PCT, we established a cut-off value of 1.84 ng/mL (sensitivity 71.4% and specificity 81.1%). However, cut-off values could not be determined for CRP and Leuk. Some investigators established different cut-off values in their studies, e.g. Schuetz *et al.* revealed a cut-off value for mortality of PCT of 0.25 µg/L with a sensitivity of 78% and a specificity of 37.76% (24). Haeuptle *et al.* established a cut-off value of PCT for mortality and hospitalization in an ICU in patients with *Legionella pneumonia* of 1.5 µg/L (25). We believe that the different cut-off values are due to the different designs of the studies. Christ-Crain and Muller emphasized that the optimal PCT cut-off values depend on a number of factors such as the clinical settings in which the study is conducted (primary care, emergency room, ICU, post-operative or trauma patients); the site and extent of the infection (respiratory tract infection, endocarditis, meningitis, others); the presence of co-morbidities (impaired pulmonary reserves, immunosuppression) and the clinical implications drawn (diagnosis, prognosis, antibiotic treatment) (6). Kutz *et al.* emphasized the role of the setting in which the study was conducted for the predictive value of PCT, too (26). They found out a higher predictive PCT value for death and other adverse events if it is used in emergency wards. In primary medical practice and in ICU, this predictive value is lower (26). In regard to MR-proADM, there is also a variation in its cut-off values. Christ-Crain *et al.* established a cut-off MR-proADM value for mortality of 1.8 nmol/L with a sensitivity of 80% and a specificity of 72% (16). An optimal cut-off value of 1.3 nmol/L with a sensitivity of 68% and a specificity of 73% was determined (9).

The cut-off values we found for both markers showed a good negative predictive value and a lower positive predictive one. This indicated that the negative test results were more important as they demonstrated a favorable outcome. If the test result is positive, the probability of an adverse outcome is lower due to the higher number of false positive results. It should be taken into account that the predictive value depends on the incidence of the event analyzed. These data referred to hospitalized CAP pa-

tients. Many of them, however, fell into the low-risk groups according to both scales, and the in-hospital mortality rate was not high. When examining another patient group (e.g. patients in the ICU), the positive predictive value would, probably, be higher. For our patients, we believe that the low levels of these two biomarkers have a better potential to predict survival compared to that of high levels to predict mortality. Krüger *et al.* also emphasize PCT role in predicting the patients with a low-risk of death (27). As a limitation of our study, we consider the relatively small number of the patients studied. Further studies are needed for better determination of the role of biomarkers in predicting the prognosis of both CAP and other infections.

CONCLUSION

MR-proADM and PCT are promising biomarkers in predicting CAP prognosis. Their predictive value for mortality is similar to that of PSI and CURB-65. CRP and Leuk can't serve as reliable predictors.

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