Original Article

Interleukin-6 and procalcitonin as biomarkers in mortality prediction of hospitalized patients with community acquired pneumonia

Ilija Andrijevic[1], Jovan Matijasevic[1], Ljiljana Andrijevic[2], Tomi Kovacevic[1], Bojan Zaric[1]

[1]Institute for Pulmonary Diseases of Vojvodina, Clinical Trials Unit, Faculty of Medicine, University of Novi Sad, Serbia, [2]Institute of Oncology, Faculty of Medicine, University of Novi Sad, Serbia

Address for correspondence:
Dr. Bojan Zaric, Institute for Pulmonary Diseases of Vojvodina, Clinic for Pulmonary Oncology, Department for Invasive Diagnostics, Clinical Trials Unit, Faculty of Medicine, University of Novi Sad, Serbia. Put Doktora Goldmana 4, 21204 Sremska Kamenica, Serbia. E-mail: bojanzaric@neobee.net

Submission: 05-01-2014
Accepted: 03-03-2014

Access this article online

Quick Response Code:

Website: www.thoracicmedicine.org

DOI: 10.4103/1817-1737.134072

Abstract:

INTRODUCTION: Community acquired pneumonia (CAP) may present as life-threatening infection with uncertain progression and outcome of treatment. Primary aim of the trial was determination of the cut-off value of serum interleukin-6 (IL-6) and procalcitonin (PCT) above which, 30-day mortality in hospitalized patients with CAP, could be predicted with high sensitivity and specificity. We investigated correlation between serum levels of IL-6 and PCT at admission and available scoring systems of CAP (pneumonia severity index-PSI, modified early warning score-MEWS and (Confusion, Urea nitrogen, respiratory rate, Blood pressure, ≥65 years of age-CURB65).

METHODS: This was prospective, non-randomized trial which included 101 patients with diagnosed CAP. PSI, MEWS and CURB65 were assessed on first day of hospitalization. IL-6 and PCT were also sampled on the first day of hospitalization.

RESULTS: Based on ROC curve analysis (AUC ± SE = 0.934 ± 0.035; 95%CI(0.864-1.0); *P* = 0.000) hospitalized CAP patients with elevated IL-6 level have 93.4% higher risk level for lethal outcome. Cut-off value of 20.2 pg/ml IL-6 shows sensitivity of 84% and specificity of 87% in mortality prediction. ROC curve analysis confirmed significant role of procalcitonin as a mortality predictor in CAP patients (AUC ± SE = 0.667 ± 0.062; 95%CI(0.546-0.789); *P* = 0.012). Patients with elevated PCT level have 66.7% higher risk level for lethal outcome. As a predictor of mortality at the cut-off value of 2.56 ng/ml PCT shows sensitivity of 76% and specificity of 61.8%.

CONCLUSIONS: Both IL-6 and PCI are significant for prediction of 30-day mortality in hospitalized patients with CAP. Serum levels of IL6 correlate with major CAP scoring systems.

Key words:

Community acquired pneumonia, interleukin-6, mortality, procalcitonin, risk assessment

Community acquired pneumonia (CAP), with its annual incidence between 0.3% and 0.5% and mortality which can be as high as 35% in hospitalized patients, represents one of the most common causes of death from infectious diseases worldwide. Unpredictable diseases course and uncertain outcome make CAP on of the major problems among lower respiratory tract infections. This makes search for the most appropriate prognostic factors and risk stratification tools one of the prerogatives in respiratory medicine. Major risk scores (PSI, CURB65) have shown to be significant advance in prediction of mortality due to CAP.[1-9] However, there are some important issues with the risk scores. PSI is more suitable for identification of low risk patients benefiting from outpatient treatment whereas CURB65 improves identification of high risk patients. PSI will underestimate risk in young adults while CURB65 will inadequately assess patient co-morbidity.[10-16] Both scales do not evaluate information about the inflammatory response of the host to infection, well known as one of the major prognostic aspects in pneumonia. Poor performance of risk scores in prediction of high risk patients is mainly caused by low positive likelihood ratios at the recommended cut-offs for 30-day mortality.[17-23]

Major prognostic drivers in CAP are respiratory insufficiency, sepsis and sepsis related organ dysfunction and unstable co-morbidities. Considering that current risk scores inadequately identify high risk patients, biomarkers are extensively investigated as additional prognostic tools. Some of the well known markers and mediators of severe infection and sepsis are interleukin-6 (IL-6) and procalcitonin (PCT). IL-6 production is initiated by inflammatory reaction induced by trauma, stress and infection. IL-6 has much longer plasma half-life than other pro-inflammatory cytokines, and that is why IL-6 serves as a very useful marker of pro-inflammatory cytokine activation. Several studies found positive correlation between

serum IL-6 concentration at admission and endmost mortality in CAP. IL6 was shown to have independent predictive value in CAP mortality. Plasmatic IL-6 concentration directly correlates with mortality risk in intra-abdominal sepsis with 82.9% accuracy for prediction of treatment outcome. PCT is also well recognized as marker of severity and outcome of infections which is especially valuable in sepsis. In some trials PCT demonstrated ability to improve mortality prediction of risk scores.[16-25]

Primary aim of the trial was determination of the cut-off value of serum IL-6 and PCT above which, lethal outcome in treatment of hospitalized patients with CAP, could be predicted with high sensitivity and specificity. We investigated correlation between serum levels of IL-6 and PCT at admission and available scoring systems of CAP (pneumonia severity index - PSI, modified early warning score - MEWS and Confusion, Urea nitrogen, Respiratory rate, Blood pressure, ≥65 years of age - CURB65) in prediction of 30-day mortality due to CAP.

Methods

This was prospective, non-randomized, longitudinal trial conducted from January 2010 to December 2012 at the Institute for Pulmonary Diseases of Vojvodina, Faculty of Medicine, University of Novi Sad, Serbia. The study was approved by the institutional review and ethics board. All of the patients enrolled in the study were informed about the trial and all signed informed consent form. Major inclusion criteria were: age over 18 years, established diagnosis of community acquired pneumonia according to IDSA (The Infectious Diseases Society of America) criteria, and chest X-ray (CXR) or thoracic CT scan suggestive for community acquired pneumonia. Exclusion criteria were: CXR or CT highly suggestive for lung cancer, hospital acquired pneumonia or health care associated pneumonia, inability to comply with protocol or refusal to participate in the study.

Standard diagnostic procedures for community acquired pneumonia (CAP) were carried out in all patients screened for the trial. There were 148 patients screened for the trial among who 101 had all inclusion criteria without any exclusions. In all patients complete blood count (CBC) with erythrocyte sedimentation rate (ESR), biochemistry panel and standard chest X-ray (CXR) followed by computerized tomography (CT) were performed. Pneumonia severity index (PSI), modified early warning score (MEWS) and CURB65 were assessed on first day of hospitalization due to CAP. Interleukin-6 (IL-6) and procalcitonin (PCT) were also sampled on the first day of hospitalization. All surviving patients underwent 30 day follow-up. The endpoint variable was death within 30 days of admission.

Quantitative measuring of human serum interleukin-6 (IL-6)

Serum samples from enrolled patients were kept conserved at −80°C until final analysis. Concentration of IL-6 was determined by commercially available kits (Quantikine HS, RandD Systems, Minneapolis, MN, USA) according to manufacturer label. Quantification kit is based on sandwich enzyme-linked immunosorbent assay (ELISA). Standards and samples were pipetted into the pools of microtitration plate. If IL-6 is present in the clinical sample it will bond with specific antibodies which coat the microtitration plate. After the washing, conjugate (specific alkaline phosphatase linked anti-IL-6 polyclonal antibodies) was added. Incubation and washing followed the procedure with subsequent addition of the nicotinamide adenine dinucleotide phosphate (NADH). Enzyme-substrate reaction led to the change in color which intensity is proportional to the amount of IL-6. Color intensity was measured by spectrophotometry. Intra assay variation coefficient was <10%. IL-6 ELISA test was with linear response ranging from 3 (low concentration) to 300 (high concentration) pg/mL. Cutoff value was 10 pg/mL.

Quantitative measuring of procalcitonin

Serum procalcitonin levels were measured by VIDAS BRAHMS PCT assay on VIDAS system (bioMérieux SA. Marcy l'Etoile, France) using ELISA technique. Normal level of PCT measured by this assay is <0.5 ng/mL.

Statistical analysis

SPSS for Windows (SPSS Inc., Chicago, IL, USA) package was used for statistical assessments. For the data analysis we used methods of standard descriptive statistics. Significance was tested by parametric and non-parametric tests (T-test and $\chi 2$ test). Kolmogorov-Smirnov test was used for testing of distribution normality. Pearson Chi-Square was used for comparison of statistical significance between categorical variables. Mann-Whitney test was used for statistical significance between continuous variables. ROC analysis was used for sensitivity and specificity assessment.

Results

There were 101 patients enrolled in this trial, 76 (75.2%) males and 25 (24.8%) females. Average age of the enrolled patients was 63.7 ± 11.8 years. Majority of patients were smokers 61 (60.4%), there was 10 (9.9%) former smokers and 30 (29.7%) non-smokers. Alcohol abuse was observed in 24 (23.8%) patients and heroin abuse was detected in 2 (2%) of patients.

In investigated group we did not find any significant correlation between demographic characteristics and 30-day mortality. There was no significant correlations between demographic characteristics and risk scores or levels of procalcitonin and IL6. Average PSI score was calculated to be 113.5 ± 41.5, ranging from 39-227, while average MEWS score was 3.8 ± 2.5. Score categories and results for CURB 65 are given in Table 1. We found significant differences in value of PSI between survivors and patients with lethal outcome (Mann-Whitney test, U = 447.5; $P < 0.01$). Significant differences between survivors and deceased patients were found in value of both CURB65 (Mann-Whitney test, U = 564.5; $P < 0.01$) and MEWS (Mann-Whitney test, U = 496.500; $P < 0.01$). After grouping the data based on Fisher's exact test we did not find significant differences between PSI <4, PSI ≥4 and outcome ($P = 0.131$). However, Fisher's exact test found significantly higher frequency of lethal outcome in group of patients with CURB65 ≥2 ($P = 0.029$) and among patients with MEWS ≥5 ($P = 0.004$) [Table 1a].

Average levels of procalcitonin (PCT), interleukin-6 (IL-6), erythrocyte sedimentation rate (ESR), white blood cell count

Table 1: PSI, CURB65 and MEWS score categories in investigated patient population

Score category/class	Number of patients	%
PSI		
I	3	3.0
II	7	6.9
III	19	18.8
IV	47	46.5
V	25	24.8
Total	101	100.0
CURB65		
0	12	11.9
1	24	23.8
2	26	25.7
3	7	16.8
4	15	14.9
5	2	2.0
6	5	5.0
Total	101	100.0
MEWS		
0-2	39	38.6
3-4	27	26.7
5-9	31	30.7
10-11	4	4.0
Total	101	100.0

Table 1a: Relation between grouped risk score data and outcome by Fisher's exact test

Score	Outcome				
	Alive		Deceased		*P*-value
	n	%	*n*	%	
PSI					
<4	25	32.9	4	16	
≥4	51	67.1	21	84	0.131
Total	76	100	25	100	
CURB 65					
<2	32	42.1	4	16	
≥2	44	57.8	21	84	0.029
Total	76	100	25	100	
MEWS					
<5	57	76	9	40.9	
≥5	18	24	13	59.1	0.004
Total	75	100	22	100	

(WBC), hemoglobin (HgB) and platelets (PLT) along with corresponding units and correlation with outcome are given in Table 2. Most of the patients had co-morbidities, 89 patients (88.1%) were diagnosed with co-morbidity. Cardiovascular disease was established in 54 (53.4%) of patients, endocrinology disorder in 20 (19.8%) and gastroenterology disease in 22 (21.8%). Surgical, respiratory, nephrology and neurology related co-morbidities were observed in 14.9%, 7.9%, 5.9% and 11.8% of the patients, respectively. We did not observe any statistically significant correlation between co-morbidities and 30-day mortality in investigated group of the patients. The co-morbidities do not correlate with any of the risk scores. Also, we did not observe any correlations between the co-morbidities and serum levels of PCT or IL6. Average duration of hospitalization

Table 2: Average levels of procalcitonin (PCT), interleukin-6 (IL-6), erythrocyte sedimentation rate (ESR), white blood cell count (WBC), hemoglobin (HgB) and platelets along with correlation to outcome and level of significance

	N	Mean	Std. Deviation	Minimum	Maximum	*t*	*P*
IL6							
alive	76	8.1708	3.88211	1.13	25.60		
dead	25	57.9688	50.80946	5.90	211.00	−8.556	0.000
Total	101	20.4970	33.12691	1.13	211.00		
HGB							
alive	76	126.51	16.035	87	157		
dead	25	121.80	17.635	96	169	1.244	0.217
Total	101	125.35	16.482	87	169		
PLT							
alive	76	263.11	106.625	31	609		
dead	25	260.60	121.960	41	494	0.098	0.922
Total	101	262.49	109.989	31	609		
WBC							
alive	76	13.548	7.6954	0.5	49.4		
dead	25	15.330	8.0216	1.0	34.6	−0.994	0.323
Total	101	13.989	7.7753	0.5	49.4		
PCT							
alive	76	7.9877	14.01199	0.05	88.80		
dead	25	13.2096	13.90698	0.13	53.40	−1.619	0.109
Total	101	9.2802	14.09959	0.05	88.80		
SE							
alive	76	51.09	28.896	5	140		
dead	25	82.96	29.295	16	124	−4.767	0.000
Total	101	58.98	31.988	5	140		

was 16 ± 9 days. Overall 30-day mortality rate of patients with community acquired pneumonia (CAP) was 24.8%.

In patients deceased due to CAP we found significantly higher levels of IL-6 ($t = -8.556$; $P < 0.01$) [Figure 1]. We did not find significant differences between alive and deceased patients in any of the other investigated parameters. Multivariate analysis of factors influencing outcome confirmed IL6 as only significant contributing factor [Table 3].

We found significant positive correlation between level of IL-6 and PSI (Spearman correlation test, = 0.366, $P < 0.01$) [Figure 2]. Significant positive correlation was also found between level of IL-6 and CURB65 (= 0.241, $P < 0.01$) and MEWS (= 0.360, $P < 0.01$) [Figures 3 and 4]. There was also significant positive correlation between IL-6 level and mortality (= 0.652, $P < 0.01$). Serum PCT did not show significant correlation with investigated risk scores, even though p-values were borderline.

The cut-off value, sensitivity and specificity of IL-6 and PCT as predictors of mortality were calculated using receiver operating characteristic (ROC) curve. ROC curve analysis defines IL-6 as certain predictor of mortality in patients with CAP. Based on ROC curve analysis (AUC ± SE = 0.934 ± 0.035; 95%CI (0.864-1.0); $P = 0.000$) hospitalized CAP patients with elevated IL-6 level have 93.4% higher risk level for lethal outcome. As a predictor of mortality at the cut-off value of 20.2 pg/ml IL-6 shows sensitivity of 84% and specificity of 87% [Figure 5]. ROC

curve analysis also confirmed significant role of procalcitonin as a mortality predictor in CAP patients (AUC ± SE = 0.667 ± 0.062; 95%CI (0.546-0.789); *P* = 0. 012). Patients with elevated PCT level have 66.7% higher risk level for lethal outcome. As a predictor of mortality at the cut-off value of 2.56 ng/ml PCT shows sensitivity of 76% and specificity of 61.8% [Figure 6].

Table 3: Multivariate analysis shows that only IL6 significantly influences the model. Increase of IL6 for one increases probability of lethal outcome for 1.275

	P	OR	95% CI
CURB65			
<2	0.890		0.143-9.422
> = 2		1.160	
MEWS			
<5	0.224		0.471-24.938
> = 5		3.428	
IL6	0.000	1.275	1.114-1.460
SE	0.115	1.022	0.995-1.051

p-p value, OR = Odds ratio, 95%CI-95% confidentiality interval

Discussion

Major demographic data in investigated group of patients are consistent with previously published data.[2-10] Most of the patients were males, average age 63.7 years, smokers with co-morbidities. Over 88% of investigated patients had co-morbidity, mainly cardiovascular (53.4%). Overall mortality rate of patients is relatively high –24.8%, mainly because we investigated patients hospitalized due to CAP, who are within higher risk score than patients treated in ambulatory setting. Most recent publication by Menendez *et al*.,[3] evaluated comparable population with majority of men with co-morbidities. This study identified age, long term care facility, neurological disease and neoplasm as significant demographic characteristics influencing mortality. We did not observe the same relation; there was no long term care facility patients in our group and we excluded patients with malignant disease from our trial. Omission to identify age as one of the strongest predictors of death in patients with CAP could be attributed to relatively small number of patients in the trial (101 total/25 deaths).

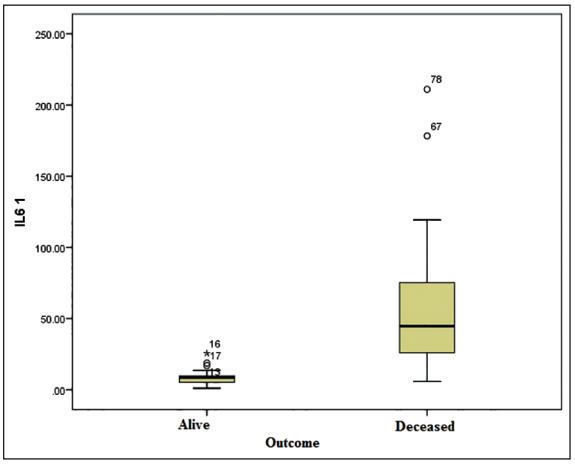

Figure 1: IL-6 level difference between CAP survivors and lethal outcome, showing significantly higher IL-6 level in deceased patients

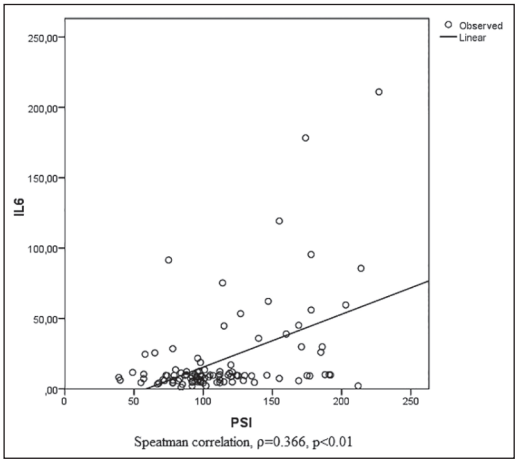

Figure 2: Significant postive correlation (Spearman correlation test, Rho = 0.366, *P* < 0.01) between IL-6 level and PSI; with the elevation of IL-6 PSI significantly rises

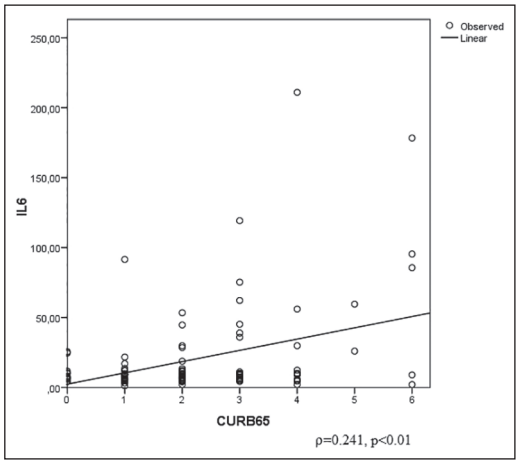

Figure 3: Significant positive correlation (Spearman correlation test, Rho = 0.241, *P* < 0.01) between IL-6 and CURB65; with the elevation of IL-6 CURB65 significantly rises

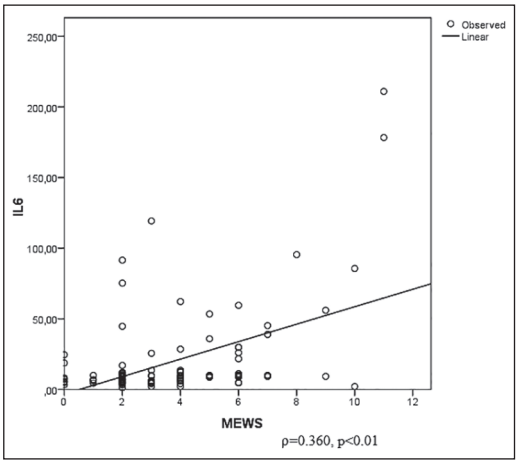

Figure 4: Significant positive correlation (Spearman correlation test, Rho = 0.360, *P* < 0.01) between IL-6 and MEWS; with the elevation of IL-6 MEWS significantly rises

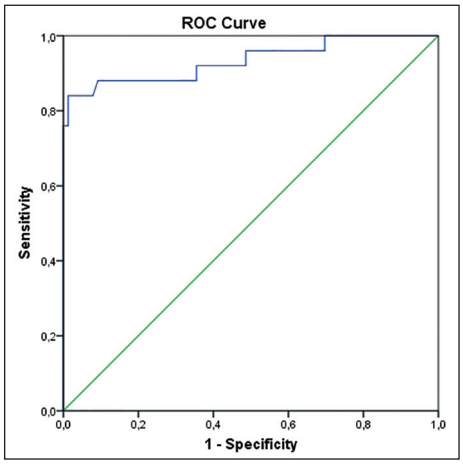

Figure 5: ROC curve diagram of IL-6 sensitivity and specificity in prediction of lethal outcome in patients with CAP (AUC ± SE = 0.934 ± 0.035; 95%CI (0.864-1.0); *P* = 0.000)

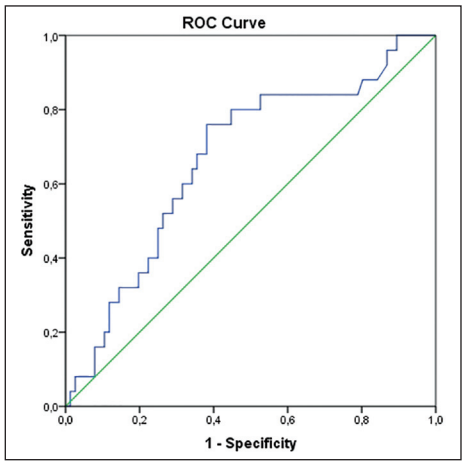

Figure 6: ROC curve diagram of PCT sensitivity and specificity in prediction of lethal outcome in patients with CAP (AUC ± SE = 0.667 ± 0.062; 95%CI (0.546-0.789); *P* = 0. 012)

Our results confirmed significant correlation between investigated risk scores and 30 day mortality in patients with CAP. Large number of patients were allocated in high PSI (IV-V) and on the contrary low CURB65 scores (0-2). MEWS was rarely investigated in the setting of mortality prediction due to CAP, primarily because it is a sepsis prediction tool. However, since patients hospitalized due to CAP have high risk of sepsis development we included MEWS score in the analysis. Majority of patients had low values of MEWS score. In investigated group of patients all three severity scores showed significant correlation with the outcome defined as 30-day mortality. In one of the most recent trials[3] same distribution of severity score categories, as reported in our trial, was found. Menendez *et al*.,[3] also found majority of patients with high PSI and low CURB65 value. We did not calculate AUC for investigated scores because primary aim of the trial was investigation of predictive value of IL-6 and PCT, however we found significant correlation between PSI, CURB65 and MEWS score and serum level of IL-6 on day one of admission. This is highly suggestive that addition of serum biomarkers to scoring systems might improve predictive value for 30-day mortality. Several trials investigated modified current scoring systems[4-8] trying to identify most appropriate modification in prediction of outcome. In current trial we did not use any modification of standard severity scores. One of the most recent meta-analyses evaluated overall performance of severity scores in prediction of mortality from CAP.[9] This analysis confirmed that PSI holds highest diagnostic odds ratio for mortality (10.77), followed by CURB65 with 6.4. Investigated populations in trials that entered this meta analysis were demographically comparable to our group-majority of males over 60 years of age. One of the major findings in this meta-analysis was pooled sensitivity and specificity for PSI and CURB65. PSI was found to have pooled sensitivity and specificity of 0.90 and 0.53, respectively. corresponding values for CURB65 were 0.62 and 0.79, respectively. It is visible that PSI shows higher sensitivity but lower specificity than CURB65. Both scales, PSI and CURB65 have low positive predictive value, 0.14 and 0.24, respectively. However, both scales have high negative predictive value, 0.98 and 0.95, respectively. It could be concluded that both scales have good negative predictive values for mortality in populations with a low prevalence of death but were less useful with regard to positive predictive values. More or less the same data were observed in a previous meta-analysis[10] on severity assessment tool for predicting mortality in hospitalized patients with CAP. These are the main reasons why biomarker assessment entered the arena of mortality prediction in hospitalized patients with CAP. Serum concentration of IL-6 at the time of admission due to CAP was found to be significantly increased (191 pg/mL vs. 73 pg/mL, $P = 0.0001$) in deceased patients hospitalized for CAP in latest trial of Menendez *et al*.[3] The same elevation in concentration of IL-6 was found in our study only with lower absolute concentration (57.96 pg/mL vs. 8.17 pg/mL, $P < 0.01$). In the same trial correlation between IL-6 and PSI was borderline insignificant with $P = 0.08$, correlation of IL-6 with CURB65 was also borderline $P = 0.054$. In our trial correlation of IL-6 and both severity scores was found to be significant with $P < 0.01$ for all three severity scores. In Menendez's trial serum PCT levels were also significantly higher in deceased patients (1.8 ng/mL vs. 0.58 ng/mL, $P = 0.002$). In our trial PCT levels in deceased patients were also higher but the difference did not reach statistical significance. Our trial did not confirm significant correlation between severity scores and PCT, while Menedez trial found such correlation and confirmed its significance. Menedez trial confirmed IL-6 and C reactive protein as independent predictive variables after adjustment for PSI and CURB65. Our trial confirmed cut-off value of IL-6 on 20.2 pg/mL above which IL-6 levels have high sensitivity and specificity in 30 day mortality prediction. One of the largest trial so far[14] defined the cut-off value of serum concentration of IL-6 for predicting a severe course of pneumonia at 27.2 pg/mL, comparable with our cut-off value for mortality. IL-6 showed sensitivity of 70.5% and specificity of 60.4% in German trial, while in our trial in prediction of mortality it reached sensitivity of 84% and specificity of 87%.

There are several limitations of this trial. Relatively small number of patients disables stratification based on PSI or CURB65 severity classes. This stratification would enable calculation of prognostic power of severity scores. However, continuation trial will soon follow. We excluded outpatient subjects from the trial, what disables us from analyzing entire CAP patient population. However, we were primarily

interested in evaluation of hospitalized patients who already had severity scores worse than outpatients. After all, there are still some important differences between Western and developing countries which might influence outcome of CAP treatment (quality of patient care, availability of antibiotics).

Conclusions

This trial confirms significant role of IL-6 and PCT in prediction of 30 day mortality in hospitalized patients with community acquired pneumonia. IL-6 shows significant correlation with major risk scores (PSI, CURB65 and MEWS) in mortality prediction. At the cut-off of 20.2 pg/mL IL-6 demonstrates high sensitivity (84%) and specificity (87%) in mortality prediction. Hospitalized patients with elevated IL-6 concentration have 93.4% increased risk of death. Patients with elevated PCT level have 66.7% higher risk level for lethal outcome. As a predictor of mortality at the cut-off value of 2.56 ng/ml PCT shows sensitivity of 76% and specificity of 61.8%.

Acknowledgement

The study was supported by the grant of the Serbian Ministry of Science and Technology, grant number 175056.

References

1. Kolditz M, Ewig S, Höffken G. Management-based risk prediction in community-acquired pneumonia by scores and biomarkers. Eur Respir J 2013;41:974-84.
2. Ewig S, Torres A. Community-acquired pneumonia as an emergency: Time for an aggressive intervention to lower mortality. Eur Respir J 2011;38:253-60.
3. Menéndez R, Martínez R, Reyes S, Mensa J, Filella X, Marcos MA, *et al*. Biomarkers improve mortality prediction by prognostic scales in community-acquired pneumonia. Thorax 2009;64:587-91.
4. Ewig S, Bauer T, Richter K, Szenscenyi J, Heller G, Strauss R, *et al*. Prediction of in-hospital death from community-acquired pneumonia by varying CRB-age groups. Eur Respir J 2013;41:917-22.
5. Xiao K, Su LX, Han BC, Yan P, Yuan N, Deng J, *et al*. Analysis of the severity and prognosis assessment of aged patients with community-acquired pneumonia: A retrospective study. J Thorac Dis 2013;5626-33.
6. van Vugt SF, Broekhuizen BD, Lammens C, Zuithoff NP, de Jong PA, Coenen S, *et al*. Use of serum C reactive protein and procalcitonin concentrations in addition to symptoms and signs to predict pneumonia in patients presenting to primary care with acute cough: Diagnostic study. BMJ 2013;346:f2450.
7. Yandiola PP, Capelastegui A, Quintana J, Diez R, Gorordo I, Bilbao A, *et al*. Prospective comparison of severity scores for predicting clinically relevant outcomes for patients hospitalized with community-acquired pneumonia. Chest 2009;135:1572-9.
8. Ewig S, Welte T. CRB-65 for the assessment of pneumonia severity: Who could ask for more? Thorax 2008;63:665-6.
9. Loke YK, Kwok CS, Niruban A, Myint PK. Value of severity scales in predicting mortality from community-acquired pneumonia: Systematic review and meta-analysis. Thorax 2010;65:884-90.
10. Chalmers JD, Singanayagam A, Akram AR, Mandal P, Short PM, Choudhury G, *et al*. Severity assessment tools for predicting mortality in hospitalised patients with community-acquired pneumonia. Systematic review and meta-analysis. Thorax 2010;65:878-83.
11. Renaud B, Coma E, Labarere J, Hayon J, Roy PM, Boureaux H, *et al*. Routine use of the Pneumonia Severity Index for guiding the site-of-treatment decision of patients with pneumonia in the emergency department: A multicenter, prospective, observational, controlled cohort study. Clin Infect Dis 2007;44:41-9.
12. Ewig S, Woodhead M, Torres A. Towards a sensible comprehension of severe community-acquired pneumonia. Intensive Care Med 2011;37:214-23.
13. Menéndez R, Sahuquillo-Arce JM, Reyes S, Martínez R, Polverino E, Cillóniz C, *et al*. Cytokine activation patterns and biomarkers are influenced by microorganisms in community-acquired pneumonia. Chest 2012;141:1537-45.
14. Zobel K, Martus P, Pletz MW, Ewig S, Prediger M, Welte T, *et al*. CAPNETZ study group. Interleukin 6, lipopolysaccharide-binding protein and interleukin 10 in the prediction of risk and etiologic patterns in patients with community-acquired pneumonia: Results from the German competence network CAPNETZ. BMC Pulm Med 2012;12:6.
15. Martínez R, Menéndez R, Reyes S, Polverino E, Cillóniz C, Martínez A, *et al*. Factors associated with inflammatory cytokine patterns in community-acquired pneumonia. Eur Respir J 2011;37:393-9.
16. Kruger S, Ewig S, Marre R, Papassotiriou J, Richter K, von Baum H, *et al*. Procalcitonin predicts patients at low risk of death from community-acquired pneumonia across all CRB-65 classes. Eur Respir J 2008;31:349-55.
17. Schuetz P, Suter-Widmer I, Chaudri A, Christ-Crain M, Zimmerli W, Mueller B. Prognostic value of procalcitonin in community-acquired pneumonia. Eur Respir J 2011;37:384-92.
18. Berg P, Lindhardt BØ. The role of procalcitonin in adult patients with community-acquired pneumonia--a systematic review. Dan Med J 2012;59:A4357.
19. Huang DT, Weissfeld LA, Kellum JA, Yealy DM, Kong L, Martino M, *et al*. Risk prediction with procalcitonin and clinical rules in community-acquired pneumonia. Ann Emerg Med 2008;52:48-58.
20. Ramirez P, Ferrer M, Marti V, Reyes S, Martínez R, Menéndez R, *et al*. Inflammatory biomarkers and prediction for intensive care unit admission in severe community acquired pneumonia. Crit Care Med 2011;39:2211-7.
21. Corrales-Medina VF, Musher DM, Wells GA, Chirinos JA, Chen L, Fine MJ. Cardiac complications in patients with community-acquired pneumonia: Incidence, timing, risk factors, and association with short-term mortality. Circulation 2012;125:773-81.
22. Ewig S, Welte T, Chastre J, Torres A. Rethinking the concepts of community-acquired and health-care-associated pneumonia. Lancet Infect Dis 2010;10:279-87.
23. Naito T, Suda T, Yasuda K, Yamada T, Todate A, Tsuchiya T, *et al*. A validation and potential modification of the pneumonia severity index in elderly patients with community-acquired pneumonia. J Am Geriatr Soc 2006;54:1212-9.
24. Niu WY, Wan YG, Li MY, Wu ZX, Zhang LG, Wang JX. The diagnostic value of serum procalcitonin, IL-10 and C-reactive protein in community acquired pneumonia and tuberculosis. Eur Rev Med Pharmacol Sci 2013;17:3329-33.
25. Paats MS, Bergen IM, Hanselaar WE, Groeninx van Zoelen EC, Hoogsteden HC, Hendriks RW, *et al*. Local and systemic cytokine profiles in nonsevere and severe community-acquired pneumonia. Eur Respir J 2013;41:1378-85.

How to cite this article: Andrijevic I, Matijasevic J, Andrijevic L, Kovacevic T, Zaric B. Interleukin-6 and procalcitonin as biomarkers in mortality prediction of hospitalized patients with community acquired pneumonia. Ann Thorac Med 2014;9:162-7.

Source of Support: Nil, **Conflict of Interest:** The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.