Role of D-dimer in predicting mortality in patients with community-acquired pneumonia

Desa Nastasijević Borovac¹, Tatjana Radjenović Petković¹, Tatjana Pejčić¹,², Ivana Stanković¹,², Irena Janković², Zorica Ćirić¹,², Milan Rančić¹,²

Clinic for Lung Diseases, Clinical Center Niš, Knez Selo¹, School of Medicine, University of Niš, Niš²; Serbia

ABSTRACT

Aim To determine whether D-dimer in patients with community-acquired pneumonia (CAP) can predict mortality risk better than standard biomarkers.

Methods White blood cell (WBC), C-reactive protein (CRP) and D-dimer in 129 patients with CAP were analyzed. The recommended Pneumonia Severity Index (PSI) score was used to classify CAP patients into five groups according to the severity of disease (Group PSI I-V), and for predicting mortality. Additionally, the patients were divided in surviving and non-surviving group.

Results White blood cell and CRP were not in correlation with the severity of CAP and the risk of mortality. The correlation between plasma D-dimer and severity of CAP was found (r=0.4993; p<0.001). The level of D-dimer was significantly higher in non-surviving (2498.38±1248.83ng/mL) than in surviving patients (966.44 ± 968.73ng/mL) (p<0.001). In predicting mortality risk, D-dimer showed sensitivity of 0.84 (cut off >1538 mg/mL), specificity 0.86 and AUC 0.859 (95%CI; 0.787–0.914). Pneumonia Severity Index in predicting of mortality risk for cut of > PSI III showed sensitivity of 0.92, specificity 0.62 and AUC 0.868 (95%CI; 0.797-0.921). There was no statistical difference between AUC of PSI and D-dimer (ΔAUC= 0.00895) (p=0.9005).

Conclusion Coagulation abnormalities were presented in older patients with severe infections and comorbidity. Plasma D-dimer correlated better than standard inflammatory markers with severity of disease and risk of mortality in patients with CAP. In predicting mortality risk, D-dimer did not show difference among the PSI score.

Key words: fibrin fragment, in-hospital mortalities, community acquired infection
INTRODUCTION

Intrahospital mortality in patients with community-acquired pneumonia (CAP) is still high. The mortality rate in CAP outpatients is 1–5%, in in-patients 12% and in intensive care patients 40% (1). Severity assessment is a crucial component in the management of patients with CAP to guide physicians in clinical decisions. Routine clinical judgments alone have shown to be a poor predictor of disease severity (2). More than 40 indicators of poor prognosis in patients with CAP have been identified, and complex scoring systems have been developed (3). The existing severity tool, Pneumonia Severity Index (PSI) incorporates various combinations (demographic characteristics, co-morbidities, clinical and laboratory variables) that are felt to be important in determining the clinical course of CAP. Pneumonia Severity Index analyzed 20 parameters (4). Testing strategies in the initial management of patients with CAP, by using PSI, predict mortality in PSI I to 0.1%, in PSI II to 0.6%, in PSI III 0.9-2.8%, in PSI IV 8.2-9.3% and in PSI V 27.0-29.2% cases (3). However, PSI score model is not practical in many clinical settings and it is not widely used (5,6).

C-reactive protein (CRP) is an acute phase protein synthesized by the liver. This protein is widely used in the management of CAP, including diagnosis, prognosis and follow-up (7,8). C-reactive protein is less precise than the Fine’s score to assess infectious pneumonia gravity but seems to be an indicator of the potential gravity of the pneumonia (9). This protein can be used as an indicator of response to treatment, but the initial concentration of this protein does not correlate closely with the severity of disease (10).

Plasma D-dimer represents an endogenous thrombotic process. The potential use of plasma D-dimer levels has been assessed as a screening test for venous thromboembolism (11). It is a non-specific test, influenced by many factors (patient’s age, background illnesses and any inflammatory state) (12). Its role in other disorders has not been defined as well. D-dimer results from the fibrin breakdown after fibrinolytic system activation by plasmin. Pro-inflammatory states in critically ill hospitalized patients lead to elevated D-dimer levels via cytokine activation of the coagulation cascade and corresponding inhibition of fibrinolysis (13). Fibrin deposition is an important feature of pulmonary infection or severe inflammation. These effects on pulmonary coagulation and fibrinolysis are regulated by various pro-inflammatory cytokines (14). Elevated pro-inflammatory cytokines are associated with the severity of pneumonia (15). Some studies suggest that an increase in D-dimer is directly related to the intra- and extra-vascular coagulation that occurs in acute and chronic lung damage in CAP cases (16).

During pneumonia, vascular congestion develops and the alveolar cavity fills with fibrin. Due to enzymatic degradation of this fibrin by the fibrinolytic system, fibrin degradation products can be released into the circulation (17). Alveolar fibrin deposition is the characteristic of diverse forms of acute lung injury. Intravascular thrombosis or disseminated intravascular coagulation can also occur in an acutely injured lung (17). Therefore, being one of the fibrin degradation products, D-dimer levels can be increased in pneumonia (17,18). Proposed scoring systems helped to distinguish patients with CAP who can be managed at home and those with high mortality risk who need intensive care treatment (3,4). Recommended score systems are accurate, but not always easy to apply in clinical practice on admission (5). The aim of this study was the assessment of the disease severity and mortality risk in patients with CAP, analyzing the correlation between D-dimer and severity of disease (by PSI score model) and mortality risk. It has hypothesized that there is a strong correlation between these parameters, and that high D-dimer value could indicate severe CAP and the high mortality risk.

PATIENTS AND METHODS

This study included 129 patients with diagnosed CAP in the period from June 2011 to February 2013 at the Clinic for Lung Diseases, Knez Selo, Clinical Center Niš, Serbia. The study was approved by the Ethics Committee of the School of Medicine, University of Niš, Serbia. All participants were older than 18 years of age and gave their informed consents. In patients with high suspicion of pulmonary embolism using helical CT scan or by lung scintigraphy were excluded. There were no patients with deep venous thrombosis, rheumatologic diseases, diagnosed pulmonary embolism, tuberculosis, anemia or pregnancy.
Blood samples were analyzed on admission. White blood cells (WBC) were evaluated via spectrophotometry method (AVL 816, USA). Serum CRP levels were evaluated via quantitative turbidimetric method (Olympus AU 400, Japan). Plasma D-dimer levels were evaluated via the quantitative latex method (Coagulomethar, ACL 2000). The physical examination findings, radiological and laboratory findings of all patients were monitored regularly.

Patients were divided into five groups according to the Pneumonia Severity Index (PSI) (4): PSI I (younger than 50 years and without co morbidity), PSI II (< 70 points), PSI III (71-90 points), PSI IV (91-130 points), PSI V (> 130 points). Based on surviving, the patients were divided into two groups: surviving group and non-surviving group.

In the statistical analysis Kruskal-Wallis and Man Whitney One Way Analysis of Variance on Ranks, and Pearson linear correlation coefficient tests were used. Receiver operating characteristic (ROC) curve was conducted in MedCalc statistical program. Diagnostic test with AUC < 0.75 was regarded as non-contributive. The comparison of the AUC of two variables was performed via the method of DeLong. Results were reported in 95% confidence interval (CI), specificity, sensitivity, area under the ROC (AUC), positive predictive value (PPV), negative predictive value (NPV), mean value, standard deviation (SD), median and percentages (%). Statistical significance was accepted at p < 0.05.

RESULTS

The study included 129 patients with CAP, an overall median age of 64.83 ± 13.32 y (77 males and 52 females) (Table 1).

<table>
<thead>
<tr>
<th>CAP</th>
<th>Number of patients</th>
<th>Median age (n ± SD) (years)</th>
<th>Sex (F/M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (PSI I)</td>
<td>11</td>
<td>39.4 ± 10.6</td>
<td>4 / 7</td>
</tr>
<tr>
<td>Group II (PSI II)</td>
<td>24</td>
<td>58.1 ± 9.4</td>
<td>14 / 10</td>
</tr>
<tr>
<td>Group III (PSI III)</td>
<td>39</td>
<td>68.9 ± 10.1</td>
<td>21 / 18</td>
</tr>
<tr>
<td>Group IV (PSI IV)</td>
<td>42</td>
<td>68.3 ± 9.9</td>
<td>11 / 31</td>
</tr>
<tr>
<td>Group V (PSI V)</td>
<td>13</td>
<td>75.3 ± 7.9</td>
<td>2 / 11</td>
</tr>
<tr>
<td>Total</td>
<td>129</td>
<td>64.8 ± 13.32</td>
<td>52 / 77</td>
</tr>
</tbody>
</table>

There was a poor linear correlation between WBC and PSI score model (r = 0.188; p = 0.03254). There was no statistical difference in WBC level by following PSI Groups (p=0.164). Statistical difference was calculated only between Group I and Group III (p = 0.035), and between Group I and Group IV (p = 0.017) (Table 2).

<table>
<thead>
<tr>
<th>CAP</th>
<th>WBC (x 10^9/L) (n ± SD) (median)</th>
<th>CRP (mg/L) (n ± SD) (median)</th>
<th>D-dimer (ng/L) (n ± SD) (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>8.79 ± 3.47</td>
<td>54.46 ± 35.37</td>
<td>346.33 ± 229.16</td>
</tr>
<tr>
<td>Group II</td>
<td>12.25 ± 6.0</td>
<td>107.51 ± 109.23</td>
<td>541.62 ± 365.45</td>
</tr>
<tr>
<td>Group III</td>
<td>12.26 ± 4.96</td>
<td>146.68 ± 97.28</td>
<td>856.64 ± 617.16</td>
</tr>
<tr>
<td>Group IV</td>
<td>13.62 ± 6.23</td>
<td>157.11 ± 98.61</td>
<td>1547.97 ± 1356</td>
</tr>
<tr>
<td>Group V</td>
<td>13.42 ± 7.23</td>
<td>199.45 ± 114.16</td>
<td>2359.46 ± 1319.43</td>
</tr>
<tr>
<td>Total</td>
<td>12.52 ± 5.81</td>
<td>140.24 ± 103.36</td>
<td>1131.05 ± 1112.58</td>
</tr>
</tbody>
</table>

*p<0.05 vs. Group III, IV and V; †p<0.05 vs. Group II and V; ‡p<0.01 vs. Group I, II and III; CAP, community-acquired pneumonia; WBC, white blood cell; CRP, C-reactive protein; PSI, Pneumonia Severity Index.

Serum CRP showed better linear correlation with PSI score model (r=0.31851; p<0.000235). There was a statistical difference in CRP value by following PSI Groups (p<0.05). There was no statistical difference between Group I and Group II (p=0.124), Group III and Group IV (p=0.633) and Group IV and Group V (p=0.235) (Table 2).

There was a higher linear correlation among D-dimer and PSI score (r=0.49922; p=0.0001). There were differences in D-dimer levels by following PSI Groups (p<0.001). There was no statistical difference of D-dimer level, only between the Group II and Group III (p=0.107) (Table 2).

In patients with CAP, 13 patients died (10.07%) (non-surviving group) and 116 patients survived (89.93%) (surviving group). All non-surviving patients had one or more comorbidities. In surviving patients 93 (80.18%) had one or more comorbidities (Table 3). All patients from Group I and Group II survived; one patient in Group III (0.26%), five patients in Group IV (11.9%) and seven patients in Group V (53.84%) did not survive.

There was no statistically significant difference among WBC level in non-surviving (13.01 ± 5.81) and surviving (12.25 ± 6.0) patients with community-acquired pneumonia (CAP) (Table 3).

<table>
<thead>
<tr>
<th>CAP</th>
<th>Number of patients</th>
<th>Median age (n ± SD) (years)</th>
<th>One or more co-morbidities (y/n)</th>
<th>Sex (F/M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-surviving group</td>
<td>13</td>
<td>74.92 ± 8.32</td>
<td>12 / 1</td>
<td>2 / 11</td>
</tr>
<tr>
<td>Surviving group</td>
<td>116</td>
<td>63.71 ± 13.33</td>
<td>93 / 23</td>
<td>50 / 66</td>
</tr>
<tr>
<td>Total</td>
<td>129</td>
<td>64.8 ± 13.32</td>
<td>116 / 12</td>
<td>52 / 77</td>
</tr>
</tbody>
</table>

CAP, Community-acquired pneumonia; SD, standard deviation; F, females; M, males;
5.85 x 10^9/L (median 11.9 x 10^9/L) and surviving patients (12.469 ± 5.83 x 10^9/L; median 11.8 x 10^9/L) (p=0.633) (Figure 1A). There was no significant difference among serum CRP levels in the non-surviving group (172.42 ± 112.73 mg/L; median 136.0 mg/L) and surviving group (138.39 ± 104.35 mg/L; median 113.0 mg/L) (p = 0.212) (Figure 1B). Plasma D-dimer level showed statistically significant difference between the non-surviving group of patients (2498.38 ± 1248.83 ng/mL; median 2188.0 ng/mL) and surviving group of patients (966.44 ± 968.73 ng/mL; median 670.00 ng/mL) (p<0.001) (Figure 1C).

White blood cell in predicting mortality risk (for cut of >16.1 x10^9/L) showed sensitivity of 38.46% (95%CI; 13.9 – 68.4), specificity of 75.86% (95%CI; 67.0 – 83.3%), positive PV=15.2 (95%CI; 5.1–31.9) and negative PV=91.7 (95%CI; 84.2 - 96.3). The area under the curve was AUC=0.541 ± 0.0868 (95%CI; 0.451–0.629), but it was non-contributive (AUC<0.75) and not statistically significant (p=0.6385) (Figure 2).

Serum CRP level in predicting mortality risk (for cut of >107.1 mg/L) showed sensitivity of 84.62% (95%CI; 54.67-98.1), specificity of 47.41% (95%CI; 38.1 - 56.9%), with positive PV=15.3 (95%CI; 7.9 - 25.7) and negative PV=96.7 (95%CI; 87.9 - 99.6). The area under the curve was AUC=0.606 ± 0.0792 with 95% confidence intervals (95%CI; 0.516 - 0.691), but it was non-contributive (AUC<0.75) and it was not statistically significant (p=0.1801) (Figure 2).

APSI score model in prediction of mortality risk (for cut of > PSI III) had sensitivity of 92.3% (95%CI; 64.0 - 99.8), specificity of 62.93% (95%CI; 53.5-71.7%), with positive PV=21.8 (95%CI; 11.8-35.0) and negative PV=98.6 (95%CI; 92.6 - 100.0). The area under the curve was AUC=0.868 ± 0.045 (95%CI; 0.797-0.921) (p<0.0001) (Figure 2).
In predicting of mortality risk in patients with CAP there was no statistical difference between the area under the ROC curves of PSI and D-dimer ($\Delta$AUC = 0.00895 ± 0.0716) (95%CI; -0.131-0.149) (p=0.9005) (Figure 2). There was a statistically significant difference between the areas under the curves of PSI and CRP in predicting mortality risk in patients with CAP ($\Delta$AUC = 0.262 ± 0.0896) (95%CI; 0.0860-0.437) (p=0.0035) (Figure 2). There was a statistically significant difference between the areas under the curves of D-dimer and CRP in predicting mortality risk in patients with CAP ($\Delta$AUC = 0.253 ± 0.0785) (95%CI; 0.0989-0.406) (p = 0.0013) (Figure 2).

DISCUSSION
This study pointed out that plasma D-dimer was correlated with the severity of CAP better than standard inflammatory biomarkers (WBC and CRP) and had almost equal result as PSI score model in predicting of mortality risk in patients with CAP. Standard routine biomarkers (CRP and WBC) on admission did not correlate with severity of the disease and patient’s outcome. Pneumonia Severity Index is a recommended model for the assessment of severity of the disease and for predicting mortality risk in patients with CAP, but although it is an accurate model, it is not so easily applicable in clinical practice (4-6).

In some studies CRP was put forward as a useful marker for predicting disease severity in patients with CAP. Mean levels of CRP on admission correlated with severity of CAP according to PSI score (19,20), and CRP <100 mg/L predict reduced risk of 30-day mortality in CAP (19). In contrast, in our study, serum CRP correlated poorly with PSI score model and severity of CAP (defined by the PSI score), there was no significant difference between CRP and WBC in surviving and not-surviving patients with CAP, and in predicting of mortality risk CRP and WBC were no contributive AUC (< 0.75). Many authors have presented the same results (21-24). C-reactive protein did not correlate with the mortality risk and severity of CAP on admission, and only daily CRP measurements are useful in monitoring the clinical course of severe CAP (25). Standard routine biomarkers (CRP and WBC) did not increase with the increasing severity of CAP, classified according to the PSI score (22).

In predicting mortality risk, it was found that CRP had AUC of 0.51 (23) and 0.59 (22), and WBC had AUC of 0.55 (22,23). C-reactive protein and WBC were not recommended as reliable admission severity markers in the guidelines (1,26).

In predicting of mortality risk PSI score model presented AUC of 0.69 (23), 0.83 (21) and 0.91 (27). In our study AUC of PSI score was 0.868, and plasma D-dimer level was high in patients with CAP depending on the severity of the disease, and it correlated with PSI score model. Other authors have also found statistically significant correlation of D-dimer levels to PSI model (27). D-dimer level <500 ng/L can identify low-risk of short-term death in patients with CAP, and increased D-dimer levels were correlated with PSI score model groups (PSI I-V) (28). Plasma D-dimer levels increases significantly with the severity of the CAP, and D-dimer levels of 2438.1 ± 2158.1 ng/mL were reported in the severe pneumonia group, and 912.6 ± 512.6 ng/mL in the non-severe pneumonia group (29). A rapid quantitative D-dimer assay at admission correlates with the severity of community acquired pneumonia (30). D-dimer levels at admission may predict the severity of CAP, and the patients with severe CAP (PSI groups IV and V) were associated with increased plasma D-dimer levels (30). In our study D-dimer level was also significantly higher in patients with PSI IV-V than in patients with PSI I-III.

Chronic elevation of inflammatory and hemostasis markers has been implicated in many age-related chronic conditions (31,32). Our patients with PSI V had the highest level of D-dimer and they were the oldest patients, and all patients from PSI V had one or more co-morbidities as well. In addition to the degree of infection, plasma D-dimer levels correlated with the age and associated diseases.

In the study with 814 patients with severe sepsis, Dhainaut et al. suggested that coagulation abnormalities contribute to organ failure and 28-day mortality (33). Plasma D-dimer levels in non-surviving patients with CAP (3786 ng/mL) were higher than in surviving patients (1609 ng/mL). Patients with CAP in PSI classes IV-V, who had plasma D-dimer levels higher than 2000 ng/mL, had a higher risk of mortality (27). In predicting risk for in-hospital mortality in patients with CAP for D-dimer >1798 ng/mL was presented AUC of 0.75 (34). We found that plasma D-dimer level was significantly higher in non-surviving pati-
In our patients with CAP, plasma D-dimer level in predicting of mortality risk, for cut of > 1538 mg/mL had AUC of 0.859. The comparison of the ROC curves of the Fine’s score (PSI score) and D-dimer did not show any difference.

In conclusion, our results supported the theory that coagulation abnormalities were common in severe community acquired pneumonia without pulmonary embolism. High D-dimer level correlated with severity of the disease and mortality.

REFERENCES


Uloga i značaj D-dimera u prognozi mortaliteta kod pacijenata s vanbolnički stečenom pneumonijom

Desa Nastasijević Borovac¹, Tatjana Radjenović Petković¹, Tatjana Pejčić²,², Ivana Stanković¹,², Irena Janković², Zorica Ćirić¹,², Milan Rančić¹,²

Klinika za plućne bolesti, Knez Selo, Klinički centar Niš¹, Medicinski fakultet, Univerzitet u Nišu, Niš; Srbija²

SAŽETAK

Cilj Odrediti da li D-dimer kod pacijenata s vanbolnički stečenom pneumonijom (VSP) može predviđati mortalitet bolje od rutinskih biomarkera inflamacije. Metode Analiziran je broj leukocita (LE), C-reaktivni protein (CRP) i D-dimer kod 129 pacijenata s VSP-om. Rezultati Broj leukocita i CRP nisu korelirali sa stepenom težine VSP-a i rizikom mortaliteta. U predviđanju mortaliteta, D-dimer ima veću senzitivnost (0,84) i specifičnost (0,86) u odnosu na PSI. Zakočeni: D-dimer je pokazao bolju korelaciju od rutinskih biomarkera inflamacije sa stepenom težine bolesti i rizikom mortaliteta. U predviđanju mortaliteta nisu ustanovljene razlike u odnosu na PSI prediktivni model. Ključne reči: D-dimer, intrahospitalni mortalitet, vanbolnički stečene infekcije


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