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PJBS

ISSN 1028-8880

Pakistan Journal of Biological Sciences

ANSInet
Asian Network for Scientific Information
308 Lasani Town, Sargodha Road, Faisalabad - Pakistan

Pakistan Journal of Biological Sciences 12 (6): 514-517, 2009
ISSN 1028-8880

On-Admission Level of Serum D-Dimer and the Severity of Community-Acquired Pneumonia

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Abstract: This study aims at evaluating on-admission serum level of d-dimer in patients with community-acquired pneumonia concerning the severity of the disease and in-hospital outcome of the patients. Sixty patients with community-acquired pneumonia were studied during a one-year period in Imam Khomeini and Sina Hospitals, Tabriz, Iran. On-admission serum d-dimer was measured by enzyme-linked immunoabsorbent assay and the severity of disease determined according to PORT grading system. In-hospital outcome was determined in regard to the level of serum d-dimer. Sixty patients with community-acquired pneumonia, 39 males and 21 females were enrolled. There were twelve patients with PORT one, eight patients with PORT two, eight patients with PORT three, twenty patients with PORT four and twelve patients with PORT five. The mean level of serum d-dimer was significantly higher in severe disease ($p<0.001$), patients with hospital stay longer than one week ($p = 0.003$), patients with bronchopulmonary pattern ($p = 0.012$), cases in-need of mechanical ventilation ($p<0.001$) and patients who expired during hospital stay ($p = 0.022$). On-admission level of serum d-dimer was significantly and independently higher in patients with severe disease ($p<0.001$) and in cases with bronchopulmonary pattern on chest x-ray ($p = 0.035$). On-admission level of serum d-dimer may predict the severity of community-acquired pneumonia. Further studies are recommended for accurate cut-off points.

Key words: Community acquired pneumonia, d-dimer, outcome, severity, mortality

INTRODUCTION

Community-Acquired Pneumonia (CAP) imposes almost 9.7 billion dollar expenses on the United States yearly and nearly 4 million adults are infected, with a 20% rate of hospitalization (Mason *et al*., 2005). Although, here is not any official report in this regard in Iran, it seems to be at least as prevalent and troublesome as in the United States. as For scheduling a treatment plan and location (out or in-patient), there 's been developed an evaluating system based on clinical, laboratory and radiological evidences that accordingly, patients are categorized in 5 groups (PORT system); grades I to III are managed out patiently and grades IV and V are hospitalized (Bartlett and Mundy, 1995). In emergency department, this method has not received an enthusiastic reception and a simply laboratory test might be suitable and more appropriate in categorizing the patients and highlighting an efficient therapeutical approach (Alvarez-Lerma and Torres, 2004). D-dimer is a specific marker produced after degradation of fibrin on activation of fibrinolytic system. In recent studies, it has been shown that d-dimer is increased in-patients with severe pneumonia and is related with a relatively higher mortality rate (Braunwald *et al*., 2005). However, the available data are limited in this regard or they are lacking consistency due to poorly designed and uncontrolled setting. We aim to use on-admission level of serum d-dimer as a primary tool for probable outcome of the patients during their hospital stay. Indeed, the main propose of current study is to investigate the relation between on-admission level of serum d-dimer as a reliable laboratory marker with the severity of CAP and advocating it, if possible, as a prognostic factor in emergency departments.

MATERIALS AND METHODS

In this descriptive-analytic cross-sectional study, 60 patients with CAP were enrolled. The study has been carried out in wards of internal infectious diseases and

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internal intensive care unit in Imam Khomeini and Sina Hospitals, Tabriz, Iran. Total duration of study is for 12 months (2007-2008). All adult patients with CAP (according to clinical signs and symptoms such as fever, chills, coughing and dyspnea; and laboratory and radiological findings) were recruited and before starting antibiotics, blood samples were taken for measuring level of d-dimer. During in-hospital stay, the PORT system was employed to grading the severity of the disease. In addition to routine anteroposterior chest X-ray, radiography of the chest was repeated in case of no clinical response to treatment or on request of the attending physician. The exclusion criteria were high suspicious pulmonary emboli, pregnancy, first six-month post-partum period, history of trauma, thrombotic stroke, or myocardial infarction during the last one month, hospitalization during the last ten days, systemic lupus erythematous, chronic renal failure on dialysis and history of antibiotic therapy during the last 48 h. For measuring the level of serum d-dimer, pretreatment sample of blood was taken and anticoagulated with citrate EDTA in presence of fibrinolytic material. Enzyme-linked immunoabsorbent assay (ELISA) was employed for quantification of serum d-dimer with Nyco Card® test. In this method, d-dimer molecules are entrapped within the membrane of related device in the wells. After that, there will be a sandwich assay interaction between these molecules and monoclonal antibodies. Presence of more than 0.1 mg of d-dimer will discolor the membrane into red. This discoloration will be more intense parallel to increasing of density of d-dimer. Nyco Card Reader II was used for reading the level of serum d-dimer. Normal level considered as <0.3 mg. Progression of chest lesion has been considered as 50% increase of its size on chest X-ray in 48 h and/or progress of segmental pneumonia to lobar form or lobar form to multilobar appearance. Written consent was taken from all the patients. This study has been approved by ethics committee of Tabriz University of Medical Science. Data were analyzed with the SPSS statistical software package (version 15.0; SPSS Inc., Chicago). Continuous variables were expressed as mean and categorical data were shown as frequency and percent. The contingency table (the Chi-square and the Fisher's exact tests where appropriate) and the independent samples t-test employed or one-way ANOVA test for comparisons (univariate studies). Statistically significant variables in a univariate study entered into a logistic regression analysis (multivariate study) for an independent predictive factor. Spearmen's rho was considered for evaluating correlations. Receiver Operator Characteristics (ROC) curve and coordinates of the curve test were employed for determining the optimal cut-off points. A p-value below 0.05 was considered significant. The odds ratio and the 95% confidence interval were used as estimates of the risk.

RESULTS

Characteristics and general information of sixty studied patients with CAP have been summarized in Table 1. Considering a cut-off point of <0.3 mg as a normal value, all the patients had abnormal levels of serum d-dimer. Mean levels of serum d-dimer in regard to different parameters are shown and compared in Table 2. Accordingly, the mean level of serum d-dimer was significantly higher in grade V disease (PORT system), patients in-need of hospital stay equal to 7 days or longer, in cases with bronchopulmonary pattern on chest X-ray, in patients supported with mechanical ventilation and in expired ones during hospitalization. In multivariate analysis, the mean level of d-dimer was not significantly and independently related to duration of hospital stay ($p = 0.412$), mortality rate ($p = 0.351$) and need of mechanical ventilation support ($p = 0.436$) which shows that the level of serum d-dimer could not predict these conditions in patients with CAP. On the other hand, two parameters which could be predicted by on-admission level of serum d-dimer were more severe disease (PORT system) ($p<0.001$) and presence of bronchopulmonary pattern on chest X-ray ($p = 0.035$). The ROC curve analysis showed that measuring of on-admission serum d-dimer in patients with CAP is applicable for predicting more than 7 days hospitalization (Area under curve = 0.718, $p = 0.004$), need of mechanical ventilation (Area under curve = 0.783, $p<0.001$) and in-hospital mortality

Table 1: Characteristics and general data of patients with community acquired pneumonia

Characteristics	Values
Gender	
Male	21(35%)
Female	39(65%)
Age (year)	47.12±12.10
Severity (PORT)	
I	12(20%)
II	8(13.3%)
III	8(13.3%)
IV	20(33.3%)
V	12(20%)
Hospital stay	
<7 days	26(43.3%)
7 days≤	34(56.7%)
Pneumonia	
Lobar	39(56.7%)
Bronchopulmonary	18(30%)
Interstitial	3(5%)
Progression of radiological pattern	19(31.7%)
Mechanical ventilation	20(33.3%)
Positive blood culture	4(6.7%)
Pleural effusion	11(18.3%)
Serum D-dimer (gL^{-1})	0.10±0.06
White blood cell (mm^{-3})	
Mean±SD	11675.00±7104.04
<4000	3(5%)
4000≤, <20000	52(86.7%)
20000≤	5(8.3%)
In-hospital mortality	12(20%)

SD: Standard deviation, MV: Mechanical ventilation

Table 2: Mean level of serum d-dimer in different groups

Parameters	Mean±SD	p-value
Gender		
Male	11.16±5.18	0.154
Female	8.95±6.38	
Severity (PORT)		
I	2.34±1.28	<0.001
II	6.44±0.98	
III	8.74±2.71	
IV	13.03±2.02	
V	17.79±1.60	
Hospital stay		
<7 days	7.97±5.70	0.003
7 days≤	12.24±4.98	
Pneumonia		
Lobar	9.15±6.14	0.012
Bronchopulmonary	13.60±3.05	
Interstitial	7.23±4.33	
Progression of radiological pattern		
Yes	8.97±5.64	0.192
No	11.05±5.65	
Mechanical ventilation		
Yes	14.07±4.35	<0.001
No	9.56±5.61	
Positive blood culture		
Yes	14.43±4.03	0.143
No	10.10±5.69	
Pleural effusion		
Yes	10.13±7.63	0.869
No	10.45±5.23	
White blood cell (mm^{-3})		
<4000	11.83±2.79	0.231
4000≤, <20000	9.93±5.88	
20000≤	14.34±2.69	
In-hospital mortality		
Yes	13.71±4.83	0.022
No	9.56±5.61	

SD: Standard deviation

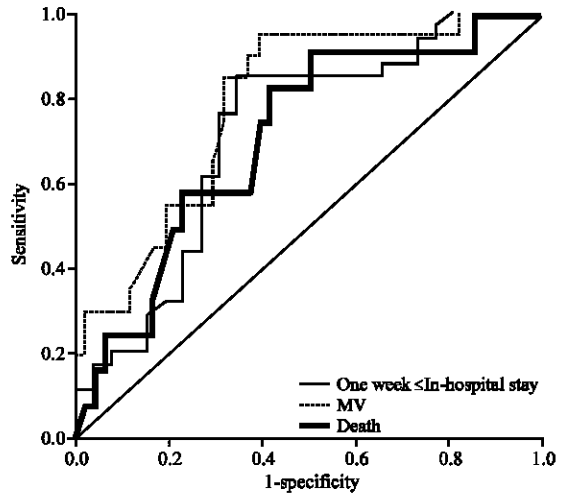

Fig. 1: Roc curves of serum level of d-dimer in predicting mortality, need of mechanical ventilation, hospital stay = one week and in-hospital mortality in patients with community acquired pneumonia

rate (area under curve = 0.714, p = 0.022) (Fig. 1). Accordingly, the best cut-off points for serum d-dimer were 8.7 mg dL^{-1} = (sensitivity = 90%, specificity = 70%), 10.55 mg dL^{-1} = (sensitivity = 90%, specificity = 70%) and 10.6 mg dL^{-1} = (sensitivity = 80%, specificity = 60%), respectively.

DISCUSSION

In the current study, sixty patients with CAP were evaluated. The level of serum d-dimer was measured in all patients on admission and before commencing administration of antibiotics by method of ELISA. It showed that the level of serum d-dimer was abnormally increased in all the patients. Analyzing the possible relation between serum level of d-dimer with different factors, it was shown that its level increases in parallel to severity of the disease according to the PORT grading system (p<0.001). Likewise, the mean level of serum d-dimer was significantly higher in patients with duration of hospitalization equal to one week or longer (p = 0.003), with pattern of bronchopulmonary on chest X-ray (p = 0.012), patients in-need of mechanical ventilation (p<0.001) and in expired cases (p = 0.022). In multivariate study, however; only sever disease (p<0.001) and presence of bronchopulmonary pattern (p = 0.035) were significantly and independently related to a higher level of serum d-dimer. In this field, there is scant number of studies available by now. Querol-Ribelles *et al.* (2004) studied 302 patients with CAP. Level of serum d-dimer was measured on day one by a quantitative latex system (Liatest D-D). Severity of disease was determined according to PSI and APACHEII systems. In this study, the level of serum d-dimer was significantly higher in patients with more severe disease. In addition, its level was significantly higher in patients with lobar or multilobar pattern on chest X-ray and in patients with progression of radiological pattern. Similar to our results, level of d-dimer was significantly higher in serum of patients in-need of mechanical ventilation and in deceased cases. In this series, the only independent parameter was mortality. In another study by Snijders *et al.* (2006), 57 patients were recruited. The severity of CAP was determined according to PSI and CURB-65 systems. There was a significant relation between the level of serum d-dimer and severity of disease. Guneysel *et al.* (2004) studied 51 patients with CAP. There was a group of healthy controls in this study, as well. The severity of disease was determined according to ATS system. The level of serum d-dimer was significantly higher in severe disease. It was significantly higher in patients comparing with the healthy counterparts. Shilon (2003) reported his results on 68 patients with CAP. The employed grading systems were PORT and APACHEII in this series. The mean level of serum d-dimer was significantly higher in patients with grades IV+V disease comparing with the patients with

grades I-III disease on the PORT system (0.0147 g L^{-1} vs. 0.0071 g L^{-1}). There was also a significant relation between the level of serum d-dimer with duration of hospital stay and mortality rate. As mentioned, there is limited number of studies in this regard. However, these studies have all reported a significant higher level of serum d-dimer on admission time of patients with severe CAP comparing with milder cases. Current findings are in line with those reports. In this study multivariate analysis was used for determination of a pure effect between serum level of d-dimer and different parameters. It showed that the predictive value of this factor for a more severe disease is independent of other coexisting conditions. On the other hand, like other mentioned reports, the level of serum d-dimer was significantly higher in expired cases and in patients in-need of mechanical ventilation support. However, these results were not obtainable in a multivariate analyzing setting. The only study similar to ours is Querol-Ribelles's. But it should be mentioned that he did not rule out any possibility of concomitant venous thromboembolism before admission. Castro *et al.* (2001) previously showed that the level of serum d-dimer is increased in patients with thromboembolic events. It was concluded that it may be impossible to distinguish these conditions from CAP in this regard. Medical history of all the patients was assessed retrospectively and any possibility of thromboembolic events in the near past was considered as an exclusion criterion. Another cause for difference might be different grading systems which have been used in studies. A previously validated PORT system was used for this purpose. At the end, it should be reminded that using of d-dimer for predicting in-hospital outcome of patient with CAP is in its first steps and further more controlled trials should be considered in this regard. According to our results, this approach is applicable, at least as a facilitating method for preparation and management of patients (McIvor, 2004). Some investigations concluded that inflammatory cytokines, especially in presence of malicious infective diseases (like sepsis), may be able of increasing level of serum d-dimer through stimulation of coagulative system (Bernard *et al.*, 2001; Bone *et al.*, 1997). In this study, there was not a significant difference of serum level of d-dimer between patients with and without positive result of blood culture ($p = 0.143$). It may be concluded that the level of this factor may be independent from mentioned inflammatory level of cytokines in other studies. It was also showed that the level of serum d-dimer is not significantly different between patients with and without pleural effusion ($p = 0.869$) or progression of chest radiological pattern ($p = 0.192$). There was not also a significant correlation between the level of d-dimer and severity of leukocytosis ($p = 0.231$). Apparently, there is not yet a similar study in these regards. Further studies with larger sample sized for a more definite conclusion (particularly for determining relevant cut-off points) are recommended.

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