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Role of D-Dimer in Assessment of the Severity of Community Acquired Pneumonia in Children

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ABSTRACT
Background: Pneumonia remains the leading cause of death in children under five worldwide. It accounts for about 1.6 million deaths a year in this age group - 18% of all deaths among children under five. More than 99% of all pneumonia deaths occur in low- and middle-income countries.
Objective: To detecting the role of D-dimer in assessment of the severity and prognosis of community acquired pneumonia (CAP) in children.
Patients and Methods: This was a cross sectional study carried out in Zagazig University Hospital, Pediatric, Microbiology and Immunology Departments. 143 children with pneumonia aged 6 months to 12 years old were included in the study that was conducted in the period from January 2019 to June 2019. Blood samples were taken from the antecubital vein with an injector and placed into citrated tubes. After they were centrifuged, the samples were evaluated with the quantitative ELISA method.
Results: The study showed that plasma D-dimer levels were higher in patients with lobar or multi-lobar pneumonia than in patients with segmental pneumonia. Additionally, the present study revealed a significant area under curve with cutoff > 0.85 and with sensitivity 97% and specificity 95% of D-dimer.
Conclusion: Pneumonia severity (CAP) patients showed increased plasma D-dimer levels in absence of an accompanying disease that could increase D-dimer levels.
Keywords: Pneumonia severity, D-dimer, Community-acquired pneumonia.

INTRODUCTION

Intrahospital mortality in patients with community-acquired pneumonia (CAP) is still high. 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 [(1)]. More than 40 indicators of poor prognosis in patients with CAP have been identified, and complex scoring systems have been developed [(2)]. 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 [(3)]. However, PSI score model is not practical in many clinical settings and it is not widely used [(4, 5)].

Plasma D-dimer represents an endogen thrombolytic process. The potential use of plasma D-dimer levels has been assessed as a screening test for venous thromboembolism [(6)]. It is a non-specific test, influenced by many factors (patient's age, background illnesses and any inflammatory state) [(7)]. 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 [(8)].

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. 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 [(9)]. Alveolar fibrin deposition is the characteristic of diverse forms of acute lung injury. Intravascular thrombosis can also occur in an acutely injured lung [(9)].

Therefore, being one of the fibrin degradation products, D-dimer levels can be increased in pneumonia. **Idelle** [(9)] and **Quick *et al.*** [(10)] 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 [(2)]. Recommended score systems are accurate, but not always easy to apply in clinical practice on admission [(4)].This study aimed to detect the role of D-dimer in assessment of the severity and prognosis of community acquired pneumonia in children.

PATIENT AND METHODS

This cross-sectional study was carried out from January 2019 to June 2019 in Zagazig University Hospital, Pediatric, Microbiology and Immunology

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Departments on 143 children with pneumonia aged 6 months to 12 years old. Written consent from parents were taken. The research was carried out in compliance with the Code of Ethics of the World Medical Association (Decleration of Helsinki) for studies involving humans.

Ethical approval:

An approval of the study was obtained from Zagazig University academic and ethical committee. Every patient signed an informed written consent for acceptance of the operation.

Inclusion Criteria: Patients recently admitted from Outpatient Clinic, cases of pneumonia diagnosed clinically.

Exclusion criteria: Patients with autoimmune diseases and patients with high suspicion of pulmonary embolism. Patients with tuberculosis and anemia. Patients under steroid therapy, patients with no previous use of antibiotics at the same illness, malignancy and blood diseases.

Patients in the study were subjected to complete history taking including name, age, gender, complaint and medical and past history. Complete clinical examination including general and chest examination that may provide clues to the diagnosis of pneumonia and/or potential complications. Examination findings must be consistent with radiography that confirmed pneumonia. Laboratory investigations (complete blood picture, C - reactive protein and D-dimer). The kit used a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) to assay the level of human D-Dimer (D2D) in samples. D-Dimer (D2D) is added to monoclonal antibody Enzyme well, which is pre-coated with human D-Dimer (D2D) monoclonal antibody incubation. Then, D-Dimer (D2D) antibodies labeled with biotin combined with streptavidin -HRP were added to form immune complex, then incubation and washing were carried out again to remove the uncombined enzyme. Then, in addition of Chromogen Solution A, B, the color of the liquid changes into the blue. Under the effect of acid, the color finally becomes yellow. The Chroma of color and the concentration of the human substance D-Dimer (D2D) of sample were positively correlated.

Calculation:

Take the standard density as the horizontal, the OD value for the vertical, draw the standard curve on graph paper. Find out the corresponding density according to the sample OD value by the Sample curve (the result is the sample density) or calculate the straight-line regression equation of the standard curve with the standard density and the OD value. With the sample OD value in the equation, calculate the sample density.

Statistical Analysis

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures were coded and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) software for analysis. According to the type of data, qualitative were represent as number and percentage and quantitative were represent by mean ± SD. The following tests were used to test differences for significance: difference and association of qualitative variable by Chi square test (X^2) and differences between quantitative independent groups by t test or Mann Whitney test. P value was set at ≤ 0.05 for significant results & < 0.001 for high significant result.

RESULTS

In this study we studied 143 child with pneumonia (70 were mild and 73 were severe) their mean age was 2.53 ± 1.71 years. Regarding sex, 90 were males and 53 were females.

Table (1): Age and sex distribution between studied groups

			Mild Group (N=70)	Sever Group (N=73)	Mann Whitney/ X^2	P
Age mean ± SD (years) median (Range)			2.49 ± 1.87 1.5 (0.5-10)	2.57 ± 1.68 2 (0.7-11.0)	-0.199	0.842
Sex	**Male**	**N**	46	44	0.45	0.501
		%	65.7%	60.3%		
	Female	**N**	24	29		
		%	34.3%	39.7%		
Total		**N**	70	73		
		%	100.0%	100.0%		

Table (1) showed no significant difference between the two groups as regards age and sex.

Table (2): CBC and CRP distribution between studied groups

			Mild Group (N=70)	Severe Group (N=73)	Mann Whitney	P
WBCs ($X10^3$)			9.93 ± 2.75	12.59 ± 3.3	-5.178	0.00**
HB (g/dl)			12.31 ± 1.43	11.92 ± 1.56	1.564	0.120
CRP (mg/l)			8.98 ± 2.6	62.0 ± 9.8	-8.594	0.00**
CRP	**-VE**	**N**	51	7	59.33	0.00**
		%	72.9%	9.6%		
	+VE	**N**	19	66		
		%	27.1%	90.4%		
Total		**N**	70	73		
		%	100.0%	100.0%		

Table (2) showed that severe group was significantly higher than mild group as regards WBCs. There was no significant difference between the two groups as regards Hb and severe group was significantly higher than mild as regards CRP.

Table (3): X-ray picture in the two groups:

			Mild Group (N=70)	Severe Group (N=73)	Mann Whitney/t	P
X-ray	**Bronchopneumonia**	**N**	42	66	39.54	0.00**
		%	60.0%	90.4%		
	Lobar pneumonia	**N**	28	7		
		%	40.0%	9.6%		
Total		**N**	70	73		
		%	100.0%	100.0%		

Table (3) showed that severe group was significantly associated with bronchopneumonia and mild with lobar.

Table (4): Complications in the two groups

			Mild Group (N=70)	Severe Group (N=73)	X^2	P
Pleural effusion	**-VE**	**N**	63	40	59.33	0.00**
		%	90.0%	54.7%		
	+VE	**N**	7	33		
		%	10.0%	45.3%		
Lung abscess	**-VE**	**N**	68	58	10.61	0.001**
		%	67.2%	79.5%		
	+VE	**N**	2	15		
		%	2.8%	20.5%		
Pneumothorax	**-VE**	**N**	65	54	9.12	0.002*
		%	92.9%	73.9%		
	+VE	**N**	5	19		
		%	7.1%	26.1%		
Empyema	**-VE**	**N**	70	63	8.31	0.003*
		%	100.0%	86.4%		
	+VE	**N**	0	10		
		%	0.0%	13.6%		
Overall	**-VE**	**N**	59	38	17.01	0.00**
		%	84.3%	52.1%		
	+VE	**N**	11	35		
		%	15.7%	47.9%		
Total		**N**	70	73		
		%	100.0%	100.0%		

Table (4) showed that severe group was significantly associated with complications.

Table (5): Heart rate, respiratory rate, temperature and SPO_2 distribution between studied groups

	Mild Group (N=70)	Severe Group (N=73)	t	P
HR (beat/min)	87.54 ± 14.25	125.91 ± 25.7	-10.977	0.00**
RR (/min)	28.12 ± 5.8	49.83 ± 14.25	-11.822	0.00**
Temp (c)	37.67 ± 0.75	38.88 ± 0.81	-9.278	0.00**
SPO_2 (%)	93.81 ± 3.71	86.41 ± 6.8	8.02	0.00**

Table (5) showed that HR, RR, Temp and SPO_2 were significantly higher in the severe group than mild group.

Table (6): D-dimer distribution between studied group

	Mild Group (N=70)	Sever Group (N=73)	Mann Whitney	P
D dimer	0.78 ± 0.62 0.6 (0.1-3.6)	5.14 ± 4.95 3.2 (0.2-19)	-6.965	0.00**

Table (6) showed that severe group was significantly higher than mild group as regards D-dimer.

Table (7): Area under curve, cutoff and validity

Area	Cutoff	P	95% Confidence Interval		Sensitivity	Specificity
			Lower Bound	Upper Bound		
0.975	>0.89	0.00**	0.747	0.994	97.0%	95.0%

Table (7) showed that significant area under curve with cutoff > 0.85 and with sensitivity 97% and specificity 95%.

Table (8): Correlation of D-dimer with other parameters

		D-Dimer
Age	**r**	-.019
	P	.820
WBCs	**r**	.284**
	P	.001
HB	**r**	-.154
	P	.066
CRP	**r**	.654**
	P	.000
RR	**r**	.368**
	P	.000
Temp	**r**	.304**
	P	.000
HR	**r**	.422**
	P	.000
SPO2	**r**	-.554**
	P	.000

Table (8) showed that D-dimer had significant positive correlation with WBCs, CRP, RR, Temp and HR but significantly negative correlated with SPO_2.

DISCUSSION

This cross sectional study was carried out in Pediatric, Microbiology and Immunology Departments, Zagazig University Hospital on 143 children with pneumonia (70 were mild and 73 were sever). Their mean age was 2.53 ± 1.71years (90 were males and 53 were females).

There was no significant difference between the two groups as regards age and sex. In agreement with our results, **Michelin *et al.*** [11] revealed that there was no significant difference between the two groups as regards age and sex, with mean age months (range) was 55 months.

The present study assessed WBCs, CRP, Hb distribution between studied groups and found that severe group was significantly higher than mild group as regards WBCs and CRP. There was no significant difference between the two groups as regards Hb. **Fares *et al.*** [12] in predicting bacterial co-infection in patients hospitalized for pneumonia found that there was no

statistical significant difference between groups regarding either WBCs or Hb and there was statistical significant difference regarding CRP. 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. C-reactive protein seems to be an indicator of the potential gravity of the pneumonia. 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 [13]. In agreement with our results, **Rasmussen and Rasmussen** [14] reported that abnormal WBC count and differential cell count determined during the first 24 hours after admission of an unselected group of acutely ill children with infections could not be used as predictions of bacterial etiology. Most children with documented viral infections had low WBC and CRP levels. In another study of **Eisenhut *et al.*** [15], high WBC, CRP levels, or both were documented in children with respiratory adenoviral infections.

There is a spectrum of radiological appearances that are consistent with the clinical and pathological diagnosis of pneumonia, ranging from complicated pneumonia (e.g. pneumonia with empyema and necrotizing pneumonia), simple or uncomplicated pneumonia (e.g. lobar consolidation) to mild interstitial changes [16]. The characteristics of childhood pneumonia in chest X-rays (CXRs) generally assume a pattern approach based on pathologic and radiologic characteristics [17].

The current study assessed CXRs findings among participant children, and revealed that severe group was significantly associated with bronchopneumonia and mild with lobar. In addition, we assessed complications between the two groups and found that there was statistical significant difference between them regarding complications with higher rates among severe group. In the study of **Søndergaard *et al.*** [18] reported that the majority of the patients (84%) had a chest x-ray taken, and 96% of these had positive radiological findings. Among infants and young children, exclusive hilar adenopathy was more frequent, while older children usually had significant peripheral infiltration on the chest X-ray.

The present study demonstrated that HR, RR, Temp and SPO_2 were significantly higher in the severe group than mild group.

D-dimer is a metabolic substance produced during the catabolization of fibrin by plasmin. D-dimer levels have been shown to increase in patients who have disorders that trigger fibrin production and catabolization. These disorders include pulmonary emboli (PE), deep vein thrombosis (DVT), solid tumors, leukemia, severe infections, trauma or a post-operative state, disseminated intravascular coagulation (DIC), pregnancy, acute stroke, sickle-cell anemia, congestive heart failure and chronic kidney failure [19]. While the measurement of plasma D-dimer levels is a well-known test for venous thromboemboli, the relationship between plasma D-dimer and other diseases is still unclear. A limited number of studies examined the relationship between CAP and plasma D-dimer levels. Some of these 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 [20]. The present study investigated the relationship between the severity of CAP and serum D-dimer levels, as well as the potential correlation among plasma D-dimer levels and revealed that severe group was significantly higher than mild group. In agreement with our study, **Arslan *et al.*** [20] found that the plasma D-dimer levels of CAP outpatients, inpatients and intensive care patients correlated positively with the severity of their pneumonia. Plasma D-dimer levels were also higher in CAP patients than in healthy controls. **Shilon *et al.*** [21] in a study performed on 68 CAP patients and no control group, classified them to five groups using pneumonia severity index and found that groups IV and V were associated with increased plasma D-dimer levels when compared to groups I, II and III. **Guneysel *et al.*** [22] studied 51 CAP patients and a healthy control group. They found D-dimer levels in the non-severe pneumonia group, severe and control groups were statistically significant. **Ribelles *et al.*** [23] found that increased plasma D-dimer levels were correlated with PSI; their results were also statistically significant. **Chalmers *et al.*** [24] also found that increased D-dimer levels were correlated with PSI.

Additionally, the present study revealed a significant area under curve with cutoff > 0.85 and with sensitivity 97% and specificity 95% of D-dimer. Several authors have addressed the relationship between D-dimer and clinical outcomes. **Querol-Ribelles *et al.*** [25] found a strong correlation between mortality rates and D-dimer in CAP, while **Kollef *et al.*** [26] demonstrated that increased D-dimer levels were associated with worse clinical outcomes.

The present study also revealed that D-dimer had significant correlation with WBCs, CRP, RR, Temp and HR but significant negative correlation with SPO_2. Several studies have examined the relationship between plasma D-dimer levels and the extent of disease in the lungs of CAP patients [23, 24]. **Levi *et al.*** [26] reported a correlation between the extent of pulmonary disease, radiological appearance and plasma D-dimer levels in severe pneumonia patients. **Ribelles *et al.*** [23] suggested that plasma D-dimer levels were higher in patients with lobar or multi-lobar pneumonia than in patients with segmental pneumonia. No relationship was detected between a high plasma D-dimer level and the radiological extent either of the disease, microorganisms present or the antibiotics previously administered and no segmental involvement was determined in the present study. This could be because the patients came to their hospital only in the later stages of the illness or because they received treatment previously in other healthcare settings. Patients were divided into two groups (lobar and multi-lobar), and plasma D-dimer levels in the multi-lobar group were significantly higher than those in the lobar group ($p < 0.05$).

In another retrospective study of **Bao *et al.*** [27] and in the overall analysis, D-dimer positively correlated with white blood cell (WBC), percentage of neutrophils, neutrophil count, C-reaction protein, high sensitive C-reactive protein (hs CRP), pro-calcitonin (PCT) and blood culture detection, but negatively correlated with lymphocyte percentage and lymphocyte count. In addition, **Guneysel *et al.*** [22] found that plasma D-dimer levels increased significantly with the severity of the CAP. A rapid quantitative D-dimer assay at admission correlates with the severity of community acquired pneumonia. D-dimer levels at admission may predict the severity of CAP, and the patients with severe CAP were associated with increased plasma D-dimer levels [21].

CONCLUSION

Pneumonia severity (CAP) patients showed increased plasma D-dimer levels in the absence of an accompanying disease that could increase D-dimer levels. Increased plasma D-dimer levels in CAP patients are correlated with the severity of the disease, WBCs, CRP, RR, Temp and HR.

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