

# Can Serum Surfactant Protein D Levels be used as an Effective Factor Instead of Clinical Severity Scores of Pneumonia in Pediatric Emergency Departments?

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## Abstract

**Aim:** To investigate whether serum surfactant protein D (SP-D) level is an applicable indicator in differentiating bacterial and viral pneumonia and determining clinical severity in cases with community-acquired pneumonia (CAP).

**Materials and Methods:** A total of 67 subjects were analyzed prospectively; of these, 32 were patients (aged 1 month–18 years) with a diagnosis of CAP and 35 were healthy control subjects.

**Results:** The median age of the patients was 17.5 months (1.5–156 months). The serum SP-D levels of the patient group were significantly higher than those of the control group ( $p < 0.001$ ). Based on the pneumonia clinical severity index, serum SP-D levels in patients with mild ( $n=7$ ), moderate ( $n=19$ ), and severe ( $n=6$ ) pneumonia were significantly higher than those in the control group ( $p < 0.001$ , respectively). The serum SP-D levels in patients with severe pneumonia were much higher than in those with mild and moderate grades based the clinical severity index ( $p < 0.001$  and  $p < 0.001$ , respectively). Although the serum SP-D levels in the bacterial pneumonia group were higher than those in the viral pneumonia group, the difference was not statistically significant.

**Conclusion:** Although serum SP-D has limited efficacy in differentiating bacterial and viral pneumonia with respect to CAP in children, it can be used as an effective bioindicator for determining the clinical severity of the disease in emergency services. (*Eurasian J Emerg Med* 2016; 15: 1-6)

**Keywords:** Community acquired pneumonia, surfactant protein D, pneumonia clinical severity index, pediatric emergency

## Introduction

Community-acquired pneumonia (CAP) in children is an important morbidity and mortality factor, especially in developing countries. According to data obtained from the World Health Organization (WHO), 156 million children under the age of five years are diagnosed with pneumonia each year. Twenty million of these children are hospitalized. More than two million are fatally affected (1, 2).

Usually, viral agents (20%–43%) are responsible for CAP etiology in children. Bacterial agents are a less significant factor (10%–40%) (3). However, many studies published in the last ten years have reported that mixed viral/bacterial infections play a role in 45% of pediatric CAP cases (4). Similar signs and symptoms caused by these agents result in the failure of radiological findings to differentiate the agents and difficulties in the routine practice of invasive interven-

tions, such as hemoculture, bronchoalveolar lavage (BAL), and lung needle biopsy. Complications resulting from these interventions have encouraged clinicians to research diagnostic and prognostic biochemical indicators in CAP cases (4, 5). Furthermore, the unnecessary use of antibiotics due to failure to perform invasive interventions based on viral and bacterial pneumonia differentiation leads to financial burdens. Consequently, differentiation is another issue that emphasizes the importance of these bioindicators.

Surfactant protein D (SP-D) is a hydrophilic protein synthesized and secreted by alveolar epithelial type 2 and Clara cells as an acute phase reactant in lung infections (6). SP-D plays an important role in host defense by recognizing the carbohydrate structures in bacteria and viruses (7). According to experimental studies, it is secreted in inflammatory lung diseases, such as lung infection and pneumonitis. SP-D levels also increase due to the deterioration of alveolar cells (8, 9).

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This study aimed to investigate whether serum SP-D levels can be used to determine clinical severity and differentiate bacterial/viral etiology in pediatric CAP cases.

## Materials and Methods

Ethical approval for this prospective study was obtained from the Local Ethics Committee of Ondokuz Mayıs University in accordance with the Declaration of Helsinki. Written informed consent was obtained from relatives of the patients. A total of 67 subjects, including 32 patients between one month and 18 years of age, were presented to the Pediatric Emergency Service of the Medical School of Ondokuz Mayıs University due to a CAP diagnosis. Thirty-five age- and gender-matched control subjects were analyzed prospectively. The diagnosis of pneumonia was established according to the criteria determined by the WHO (10). Clinical severity scores were determined using the clinical severity index of Liu et al. (11), which is based on respiratory rate, retraction, the presence of dyspnea, and findings of auscultation (Table 1). To differentiate bacterial and viral pneumonia, modified parameters of the study conducted by Ruuskanen et al. (5) were used as pneumonia etiology prediction scores (Table 2). According to this scoring system, cases with scores <3 were evaluated to have viral etiology. Those with scores ≥3 were evaluated to have bacterial etiology. The cri-

teria of the guidelines of the British Thoracic Society were used in making hospitalization decisions (12). Patients were excluded from the study if they had a medical history of different diseases that may affect serum SP-D levels (including chronic pulmonary diseases such as cystic fibrosis, asthma, bronchiolitis obliterans, and bronchopulmonary dysplasia, as well as hepatic, renal, gastrointestinal, hematological, endocrinological, metabolic, neurological, or cardiovascular disorders). The control group consisted of healthy age- and gender-matched children.

The demographic characteristics, clinical, laboratory and radiological findings, serum SP-D levels, pneumonia clinical severity index results and patient treatment responses were evaluated. The correlation of other variables used for pneumonia clinical severity indexes, pneumonia etiology prediction scores with serum SP-D levels and C-reactive protein (CRP), leukocyte, sedimentation, neutrophil and lymphocyte counts, were analyzed.

### Collection of the Serum Samples and Measurement of Serum SP-D levels

Serum samples were allowed to clot spontaneously at room temperature and were centrifuged at 3000 ×g for 10 min. All samples were stored at -80°C pending analysis of serum SP-D. Serum SP-D levels were evaluated using ELISA (catalog no: RD194059101, BioVendor, European Union). Results were recorded in ng/mL.

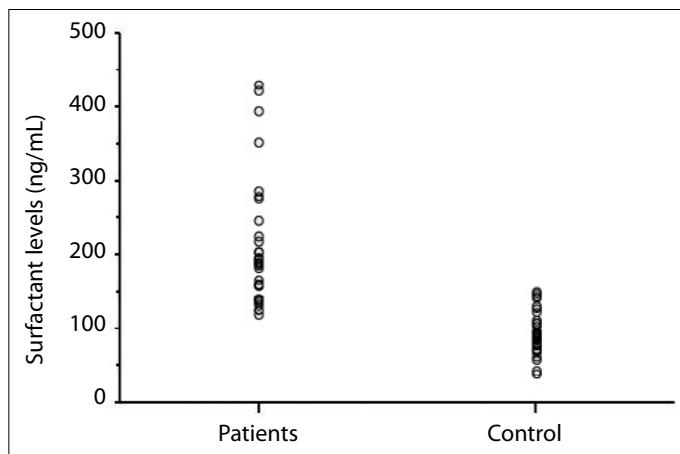
**Table 1.** Clinical score for severity of pneumonia (11)

Variables	Clinical score, circle one			
	0 point	1 point	2 points	3 points
	<b>Respiratory rate*</b>			
Age				
<2 m		≤60	61–69	≥70
2–12 m		≤50	51–59	≥60
13 m–2 y		≤40	41–44	≥45
25 m–3 y		≤34	35–39	≥40
37 m–5 y		≤30	31–34	≥35
61 m–12 y		≤26	27–30	≥31
>12 y		≤23	24–27	≥28
Retractions	None	Intercostal	Intercostal and substernal	Intercostal, substernal, and supraclavicular
Dyspnea				
0–2 y	Normal feeding, vocalizations, and activity	Any 1 of the following: difficulty in feeding, decreased vocalization, or agitation	Any 2 of the following: difficulty in feeding, decreased vocalization, or agitation	Stops feeding, does not vocalize, or is drowsy or confused
25 m–5 y	Normal feeding, vocalizations, and play	Any 1 of the following: decreased appetite, increased coughing after play, or hyperactivity	Any 2 of the following: decreased appetite, increased coughing after play, and hyperactivity	Stops eating or drinking, stops playing, or is drowsy or confused
≥5 y	Counts till ≥10 in one breath	Counts till 7–9 in one breath	Counts till 4–6 in one breath	Counts till ≤3 in one breath
Wheeze	Normal breathing; no wheezing present	End-expiratory wheeze only	Expiratory wheeze only (greater than end-expiratory wheeze)	Inspiratory and expiratory wheeze, diminished breath sounds, or both

\*(breaths/min), count respiratory rate for one full minute while patient is awake; m: months; y: years

**Table 2.** Clinical and laboratory variables used to distinguish viral pneumonia from bacterial pneumonia (pneumonia etiology prediction score) (5)

Parametres	0 point	1 point
Age	<5 years	≥5 years
Clinical profile	Rhinitis, wheezing	>38.5 °C fever, tachypnea
Total white blood cell count	<15×10 <sup>9</sup> cells per L	≥15×10 <sup>9</sup> cells per L
Serum levels of C-reactive protein	<20 mg/L	≥20 mg/L
Chest radiograph findings	Sole interstitial infiltrates, bilaterally	Lobar alveolar infiltrates
Response to antibiotic treatment	Slow or non-responsive	Rapid (in three days)
Total score: ≥3 suspected bacterial, <3 suspected viral		

**Figure 1.** Comparison of serum SP-D levels between patient and control groups

### Statistical analysis

All parameters were analyzed using the Statistical Package for the Social Sciences software version 21.0 (IBM SPSS Statistics; New York, USA). Control of normal data distribution was performed using the Shapiro–Wilks test. All categorical variables were represented as numbers and percentages, whereas numerical variables were given as mean±standard deviation and median (minimum–maximum). The normally distributed values of the patients and controls were compared using the independent t test, while non-normally distributed data were analyzed using the Mann–Whitney U and Kruskal–Wallis tests. Pearson’s chi-square test was used to analyze categorical data. Correlations between quantitative data were analyzed using the Spearman’s correlation test. The accepted value for statistical significance was  $p < 0.05$ .

### Results

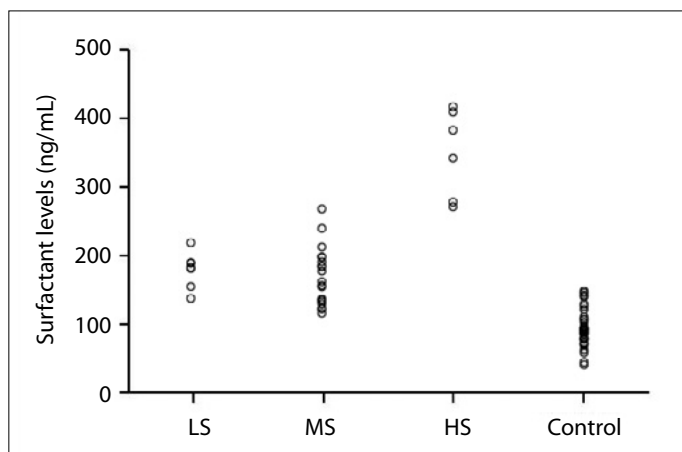
The study included 67 total subjects, consisting of 35 healthy control subjects and 32 patients who applied to the Pediatric Emergency Service of our hospital with a CAP diagnosis. The median age of the patient group was 17.5 months (1.5 to 156 months), and the

**Table 3.** Comparison of serum SP-D levels in all study groups

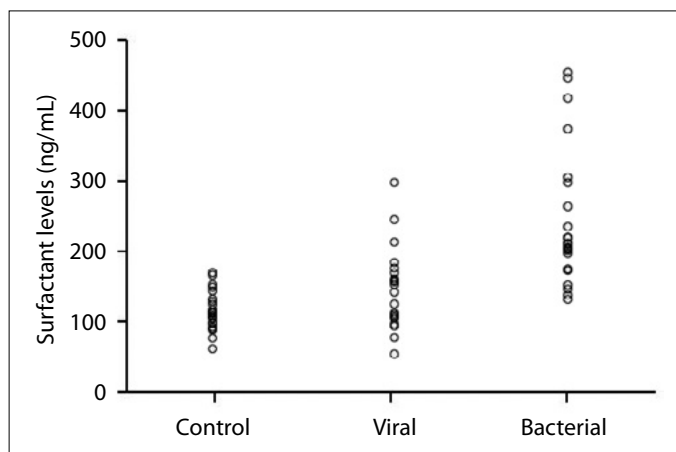
Groups	n	SP-D (ng/mL)*	p
Control	35	93.79 (39.66–154.27)	<0.001
Patients	32	192.92 (120.24–440.81)	
<b>According to the SPS</b>			
LS	7	191.31 <sup>A</sup> (143.16–229.64)	0.001
MS	19	169.07 <sup>A</sup> (120.24–282.09)	
HS	6	382.67 <sup>B</sup> (285.30–440.81)	
<b>According to the PEPS</b>			
Viral	9	132.59 (39.66–282.09)	0.133
Bacterial	23	198.22 (120.24–440.81)	
*median (min-max), SP-D: surfactant protein D; LS: low score; MS: moderate score; HS: high score; SPS: severity of pneumonia score; PEPS: pneumonia etiology prediction score.			

median age of the control group was 24 months (1 to 156 months). The female/male ratio of the patient group was 1:13 (17/15), with a 1:18 (19/16) ratio in the control group. No difference was found between the groups with respect to median age value and gender ( $p=0.183$  and  $p=0.559$ , respectively). 24 patients (75%) received oxygen therapy during a follow-up period with a median duration of 2 days (between 0.5 and 27). One patient was intubated and hospitalized in the intensive care unit. 27 total patients applied with fever (84.3%) for a median duration of two days (between one and nine days). All patients received antibiotics for a median duration of five days (between 2 and 42 days). Complications such as parapneumonic pleural effusion requiring no drainage, atelectasis, and respiratory acidosis were detected in 2 (6.2%), 8 (25%), and 11 (34.3%) of the cases, respectively. The mean hospitalization duration of the patients was  $11.72 \pm 8.25$  days (2 to 42 days).

Serum SP-D levels were significantly higher in the patient group than in the control group ( $p < 0.001$ ) (Figure 1, Table 3). According to the pneumonia clinical severity index, serum SP-D levels in the groups with mild ( $n=7$ ), moderate ( $n=19$ ), and severe ( $n=6$ ) pneumonia were significantly higher than in the control group ( $p < 0.001$ ,  $p < 0.001$ , and  $p < 0.001$ , respectively) (Figure 2 and Table 3). While there was no significant difference between serum SP-D levels in cases with mild and moderate clinical severity ( $p=0.461$ ), serum SP-D levels in cases with a severe clinical index were remarkably higher than in cases with mild and moderate clinical severity ( $p < 0.001$  and  $p < 0.001$ , respectively) (Figure 2 and Table 3). No significant correlation was found between clinical severity index and C-reactive protein (CRP) or thrombocyte and neutrophil counts ( $p=0.942$ ,  $p=0.328$ , and  $p=0.429$ , respectively). Serum SP-D levels were higher in the groups with bacterial etiology. However, the difference was not statistically significant ( $p=0.133$ ) (Figure 3 and Table 3). A significant correlation ( $r=0.482$ ,  $p < 0.001$ ) was found between serum SP-D level and hospitalization duration in patients with bacterial etiology, whereas no sig-



**Figure 2.** Comparison of serum SP-D levels according to pneumonia severity scores (LS: low score; MS: moderate score; HS: high score)



**Figure 3.** Comparison of serum SP-D levels according to pneumonia etiology prediction scores

**Table 4.** Comparison of clinical and laboratory findings in all patients according to pneumonia etiology prediction scores

Variables	Bacterial (n=23)	Viral (n=9)	p
Age, median (range)	21 months (1.5–156)	2.5 months (1.5–45)	0.262
Gender			
Male, n (%)	11 (47.8)	4 (44.4)	0.853
Female, n (%)	12 (52.2)	5 (55.6)	
Fever, (mean±SD)	37.10±0.78 °C	36.83±0.45°C	0.331
Total white-blood cell count (mean±SD)	13450±8041 cells/L	14081±7122 cells/L	0.838
Neutrophil count, (mean±SD)	61.7±18.9%	41.0±19.7%	0.114
CRP, median (range)	38.7 mg/L (0.5–270.0)	15.0 mg/L (1.0–29.0)	0.416
Wheezing, n (%)	7 (30.4)	6 (66.7)	0.109
Ral, n (%)	22 (95.7)	8 (88.9)	0.490
Retractions, n (%)	20 (87.0)	7 (77.8)	0.604
Nasal flaring, n (%)	19 (82.6)	6 (66.7)	0.370
Cyanosis, n (%)	5 (21.7)	1 (11.1)	0.648
Oxygen saturation, median (range)	86.2% (43.0–99.6)	82.7% (77.0–97.6)	0.081
Oxygen therapy requirement, n (%)	19 (82.6)	5 (55.6)	0.176
Respiratory acidosis, n (%)	9 (39.1)	4 (44.4)	0.688
Intubation, n (%)	1 (4.3)	-	
Radiological findings			
Sole interstitial infiltrates, bilaterally, n (%)	5 (21.7)	7 (77.8)	0.118
Lobar alveolar infiltrates, n (%)	11 (47.8)	1 (11.1)	0.109
Atelectasia, n (%)	7 (30.4)	1 (11.1)	0.386
Pleural effusion, n (%)	2 (8.7)	-	
Length of hospitalization, median (range)	12 (6–42) days	6 (2–10) days	<0.001

CRP: C-reactive protein; SD: standard deviation

nificant correlation was detected ( $r=0.183$ ,  $p=0.638$ ) in patients with viral etiology. When the clinical, radiological, and laboratory findings were compared to pneumonia etiology prediction scores, a significant difference in hospitalization duration was detected between

the bacterial and viral etiology groups ( $p<0.001$ ) (Table 4). No significant correlation was found between serum SP-D level and CRP, total WBC, or neutrophil count ( $r=0.064$ ,  $p=0.773$ ;  $r=0.221$ ,  $p=0.310$ ; and  $r=0.339$ ,  $p=0.114$ , respectively).

## Discussion

This study investigated the efficacy of serum SP-D levels in predicting clinical severity, prognosis, and pneumonia etiology in children with CAP who were presented at our Pediatric Emergency Service.

Serum surfactant protein is a hydrophilic protein from the collectin family, secreted by alveolar epithelial type 2 and Clara cells in the lung tissue (6). SP-D is secreted as an acute phase reactant, especially in the presence of infectious agents; it plays a role in host defense mechanisms via adhesion to micro-organisms due to its hydrophilic nature (6, 7), is important in aggregation, neutralization, and opsonization during phagocytosis, results in direct gram-negative bacterial cell-membrane lysis, inhibiting bacterial/fungal growth in macrophages, and has an aggregation-independent manner (7, 13). Therefore, SP-D is an important biomarker of infectious pulmonary diseases. Studies have shown that it plays an important role in host defense against viral and bacterial CAP agents, such as *Klebsiella pneumoniae* (14, 15), *Haemophilus influenza* (14, 16), *Streptococcus pneumoniae* (14, 17), *Mycoplasma pneumoniae* (14, 18), and influenza A virus (14, 19).

Etiology clarification (bacterial or viral) in CAP cases is important for pneumonia management. Despite advanced diagnostic tests, a clinical algorithm has not yet been developed to clarify etiology in the child age group. Specifically, high coinfection rates (30 to 45%) accompanying viral CAP cases increase the difficulty of this situation (4, 5). Unclarified CAP etiology is critical, since it leads to unnecessary use of antibiotics, elevated resistance, and increased health care expenses. Diagnostic difficulties in CAP cases generally necessitate the evaluation of multiple factors to differentiate viral and bacterial etiology, such as patient age, disease progression, accompanying symptoms, serum biomarkers, serum acute phase reactants, radiological findings, presence of viral epidemics, and clinical response to antibiotics (5). For that purpose, the British Thoracic Society has emphasized that viral pneumonia should be considered in the presence of a fever under 38.5 °C, wheezing, a respiratory rate below 50/min, and striking chest recession for children under five years old (20). In our study, we used the scores of the variables identified by Ruuskanen et al. (5) to differentiate viral and bacterial pneumonia and investigate whether serum SP-D value can be used solely as a marker in this etiological differentiation.

The markers used in biomarker studies of CAP cases include inflammatory indicators such as CRP, WBC, ESR, procalcitonin, IL-6, and TNF- $\alpha$  (5, 21, 22). The conclusions of studies vary with respect to the success of these inflammatory indicators in predicting clinical severity in patients diagnosed with pneumonia. Serum WBC, CRP, and procalcitonin levels are the most widely studied acute phase reactants in child and adult CAP cases (5). The literature has demonstrated significantly higher levels in subjects with bacterial pneumonia, though this indication does not show sufficient specificity or sensitivity when used exclusively (5). Another study conducted by Christ-Crain et al. (23) revealed that C-reactive peptide (CRP) does not show a significant difference in pneumonia cases with different severity degrees assessed by PSI. However, CRP has been identified as a serum marker in predicting bacterial pneumonia in another study conducted by the Pediatric Emergency Service (24). Kolling et al. (25) have shown that IL-1  $\beta$  levels in CAP patients are not correlated with inflammatory markers, such as WBC and CRP, in contrast to IL-1 $\alpha$  and TNF- $\alpha$ .

However, IL-1  $\beta$  levels are more correlated with clinical pulmonary infection scores. These studies have stated that ESR and WBC, as well as the other acute phase reactants, are most commonly used in clinical practice to demonstrate moderate sensitivity and specificity as well as low diagnostic efficacy (22, 26–28). In this study, no significant correlation was found between the clinical severity index and CRP, WBC, and neutrophil compatibility. However, these markers were observed to be statistically significant in the differentiation of viral and bacterial pneumonia.

In recent years, experimental studies have emphasized that specific pulmonary bioindicators considered to be secreted from deteriorated lung tissue, such as surfactant protein A (SP-A), surfactant protein D (SP-D), Krebs von den Lungren-6 (KL-6), and Clara cell protein (CC-16), are effective in determining lung deterioration severity (29–31).

In a study on adult CAP cases, Leth-Larsen et al. (14) reported that they could only determine the agent in 22 (36%) of 61 CAP cases. Furthermore, they detected that serum SP-D levels were higher in pneumonia cases with atypical etiology than in pneumonia cases associated with *Streptococcus pneumoniae* and *Haemophilus influenza* as etiological agents, in contrast to CRP and WBC, according to etiological detection results in these cases. A study by Ichiyasu et al. (31) on 48 cases of bronchopneumonia with or without chronic asthma in an age group ranging from two to four years revealed that serum SP-D levels were higher in severe cases requiring intensive care. In another study on 53 cases with RSV bronchiolitis with or without chronic heart disease, Mosbah et al. (32) detected that serum SP-D levels were higher in the patient group, which required mechanical ventilation support and oxygen requirements. These two studies indicate that serum SP-D level increases in severe pulmonary infection with either bacterial or viral etiology. In addition, Shu et al. (33) suggest investigating the correlation between lung involvement and serum SP-D levels. Their study on serum SP-D levels in 47 CAP cases attributes this conclusion to the fact that *Mycoplasma pneumoniae* in children correlates to SP-D levels detected by BAL and increases significantly when accompanied by severe lung involvement. This study indicates the validity of using serum SP-D levels rather than interventional diagnostic methods such as BAL to differentiate lung infection etiology. Our research revealed that serum SP-D levels increase according to lung infection severity. This is compatible with the literature concerning viral and bacterial etiology cases. Nevertheless, research has established that the SP-D level increase in CAP cases with bacterial etiology was higher than in cases with viral etiology. However, this difference was not statistically significant.

### Study limitations

This study had several limitations. For example, it was conducted at one referral center with a limited number of patients over a short time period.

### Conclusion

Serum SP-D levels in children are applicable biomarkers that can help to predict severity in CAP cases applying to pediatric emergency services. Furthermore, prospective studies must be conducted on larger case series. A higher increase in serum SP-D levels in cases of bacterial pneumonia is demonstrated; however, clinical applications related to differentiating bacterial and viral pneumonia are limited.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Ondokuz Mayıs University School of Medicine.

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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