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Title: The Relationship between Serum Endocan Levels and Childhood Community-acquired Pneumonia

Short title: Serum endocan level in childhood pneumonia

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Abstract

Objective: Community-acquired pneumonia is a potentially lethal lower respiratory tract infection for children. For this reason, it is important to recognize the disease early and to treat it appropriately and also we need to determine which patient will be hospitalized or not hospitalized. We aimed to evaluate plasma endocan level for determining the whether is it effective in giving the decision of hospitalization and the assessment of the response to treatment in patients with CAP.

Material and Methods: This prospective case-control study was conducted between November 2015 and May 2016 at Erciyes University School of Medicine. Fifty-three patients, who were diagnosed with CAP with clinical and radiological findings. The patients were divided into various subgroups such as inpatient, outpatient, complicated, no-complicated, and dead patients etc. and the levels of endocan were compared between the control group and their own.

Results: Total 53 children with a diagnosis of CAP and 55 healthy children were enrolled in the study. Patients were divided into two groups: hospitalized patients and outpatient groups. There was no statistically significant difference between these groups' serum endocan levels on the first day and serum endocan levels on the fourth day ($p=0.783$, $p=0.419$)

Conclusion: Serum endocan level had no significant value in determining patients' hospitalization. On the other hand, high serum endocrine levels may be significant in determining the severity of the disease and poor prognosis

Keywords: Community-acquired pneumonia, hospitalization, Endocan

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Introduction

Community-acquired pneumonia (CAP) is defined as a clinical diagnosis of pneumonia caused by an infection acquired outside hospital in a previously healthy child¹. CAP is a potentially lethal lower respiratory tract infection, affecting children all over the world². For this reason, it is important to recognize the disease early and to treat it appropriately as well as being able to determine which patients need to be hospitalized, which is a decision based on clinical findings however; these findings may change according to the clinician's experience. Sometimes there might be difficulties in the detection of clinical symptoms in busy emergency departments and hospitals. Although markers such as ESR (erythrocyte sedimentation ratio), CRP (C - reactive protein), PCT (procalcitonin), cytokines, and leukocyte counts are examined, none of them have specific characteristics in pneumonia screening or on the decision to hospitalize a patient. Serum levels may increase in other inflammatory events and infections. Studies have shown that serum PCT levels and some cytokines (IL-6) are associated with the prognosis of the disease³. However, there is currently no specific marker for identifying disease severity and in the hospitalization decision of CAP in children⁴.

Endocan, also known as endothelial cell-specific molecule-1 (ECM-1), is a peptidoglycan synthesized in endothelial cells. It is also a sign of endothelial activation, as well as of endothelial-associated pathogens⁵. Endocan is secreted from activated endothelial cells, particularly from the lung and less frequently from renal vessels and tumour endothelial cells. Control of the secretion of endocan is mediated by cytokines and growth factors. Factors such as IL-8, TNF- α , IL-1 β , e-selectin, and Vascular Endothelial Growth Factor (VEGF) increase the secretion of endocan but IFN- gamma inhibits its

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secretion^{6, 7}. There is approximately 1 ng / ml of endocan in the blood of healthy people but serum levels are increased in cases of infection such as septic shock and in cancer diseases⁸.

In this study, the aim was to evaluate plasma endocan levels at the time of admission, on the fourth day of treatment in children with CAP, and to examine its relationship with commonly used markers such as CRP, WBC (white blood cell), and neutrophil count. Furthermore, the effect of endocan, which is released in lung tissue and increased in the infections, was evaluated in the determination of disease severity, effects of hospitalization, and the assessment of the response to treatment in patients with CAP.

Methods:

This prospective case-control study was conducted between November 2015 and May 2016 in Erciyes University School of Medicine, Department of Paediatrics Pulmonology unit. Fifty-three patients, diagnosed with CAP with clinical and radiological findings, had not been treated previously, and aged between 3 months and 18 years of age were included in the study. CAP, diagnosed by a paediatrician, was defined by the association of clinical symptoms (i.e. fever >38.0 °C, coughing, dyspnea, tachypne, and pleuritic chest pain), physical examination findings (i.e crackles (rales), retractions, and rhonchus), and chest X-ray⁹. If there were suspicious radiological findings, a paediatric radiologist was consulted. If the patients had these defined features, they were enrolled in the study.

The patients were separated into two groups of outpatient and hospitalized patients according to the Clinical Practice Guidelines of the Paediatric Infectious Diseases Society of America (4). Patients were treated using the most recent guideline and after the disease was cured, they were discharged from

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the hospital. Patients, who were treated without hospitalization, were checked on the fourth day of treatment and 2 weeks later. All of the patients' routine examinations were done. These patients did not have any problems in their follow-up and all of them were cured. Eighty patients with CAP were initially included however, 27 patients, who did not come for check up on the fourth day, were excluded from the study.

Exclusion criteria were as follows: age <3 months, > 18 years, cystic fibrosis, bronchiectasis, tuberculosis, immotile cilia syndrome, sickle cell anaemia, Down syndrome, cerebral palsy, acute / chronic renal insufficiency, acute / chronic liver failure, congenital heart disease, patients who were previously treated at other locations, those with multiple antiepileptic and immunosuppressive treatment, chemical pneumonia, hospital-acquired pneumonia, and ventilator associated pneumonia. 55 healthy children who came to the hospital for routine examinations were enrolled in the study as the control group.

Blood samples for endocan were taken at the time of diagnosis and on the fourth day of treatment. They were placed in EDTA tubes and then centrifuged for 10 minutes at 2,000 g. Then, the plasma samples were stored at -80°C until the time of analysis. Hemogram, CRP, ESR, and blood cultures were performed and studied the same day. Levels of endocan were determined in duplicate by using enzyme-linked immunosorbent assay kits (Yehua brand ELISA kit cat no: YHB1079HU). CRP was determined with a Siemens brand BN-II device by the immunonephelometric method in xxxx University Hospital, Central Laboratories

Statistical analysis:

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Statistical analysis was performed using the SPSS (Statistical Package for Science Studies) version 22.0 for Windows. Variables were stated as means with maximum -minimum or median with the 25th and 75th percentile. The Pearson Chi-Square test was used to compare qualitative data as well as descriptive statistical methods (mean, standard deviation, and frequency). The distribution of the data was evaluated by histogram, q-q graphs, and the Shapiro-Wilk test. The difference between the two groups without normal distribution was compared with the Mann-Whitney test. The Wilcoxon Signed Ranks test was used for comparison of two dependent groups for variables without normal distribution. The Kruskal-Wallis test was used to compare the medians when the number of cases in the groups was not equal. P value ≤ 0.05 was considered to be statistically significant. The Dunn-Bonferroni correction was applied for multiple comparisons. The receiver operating characteristic curve (ROC) was used to assess the sensitivity and specificity of the markers. The area under the curve (AUC) was used to calculate the predictive value of the markers for pneumonia. The data was evaluated using programs R3.2.2 (www.r-project.org) and easyROC (www.biosoft.hacettepe.edu.tr/easyROC).

Ethics: All procedures were approved by the ethics committee at University (number: 96681246/192).

Informed consent: All patients and control groups were informed about the steps of the study and written informed consent was obtained.

Results:

Fifty-three children with CAP and 55 healthy children were enrolled in the study. The demographic data of the patients are summarized in table 1. There was no statistically significant difference in age and gender between the patient and control groups ($p = 0.429$ for age and $p = 0.546$ for gender). Thirty-

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eight patients (71.6%) were hospitalized and treated; 15 patients (28.4%) received medical treatment at home. Complications developed in 15 (28.3%) patients, which were hospitalized, and three (5.7%) died. Twelve (22.6%) of the complicated cases were of pleural effusion, there was one case of HUS (haemolytic uremic syndrome), and two cases of abscess. Six (11.3%) patients were admitted to the intensive care unit because of MV (mechanical ventilation) requirements. One of the patients was followed up by non-invasive MV and 5 by invasive MV. There was no statistically significant difference between the serum endocan levels on the first day of the patient and control group ($p=0.400$) (Table 2).

The first and fourth days, plasma endocan levels of the patient group were evaluated. There was no statistically significant difference between the plasma endocan levels ($p = 0.155$) (Table 2). There was no statistically significant difference between the hospitalized or outpatient groups serum endocan levels on the first day and serum endocan levels on the fourth day ($p=0.783$, $p=0.419$) (Table 2). When we assessed endocan levels according to the clinical status of the patients, serum endocan levels were higher in the patients that died than the other patients on the fourth day [1st day 0.32 (0.25- 0.36) ng/ml, 4th day 0.71 (0.69-1.34) ng/ml, versus 0.54 (0.33-1.30) ng/ml, 0.48 (0.29-1.3) ng/ml]. In addition, the patients, who needed MV, serum endocan levels were higher than other patients [1st day 0.80 (0.19-2.65) ng/ml, 4th day 1.58 (0.68-1.96) ng/ml, versus 0.52 (0.19-2.98) ng/ml, 0.43 (0.17-2.47) ng/ml]. Microorganisms were detected in the blood cultures of 6 patients. The median serum endocan levels of these 6 patients were 0.75 (0.19-2.48) ng / ml for the 1st day, 1.62 (0.29-2.28) for 4th day, and 0.52 (0.19-2.89) ng / ml for the 1st day, 0.48 (0.17-2.47) for the 4th day in blood culture negative patients (Table 2)

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The white blood cell count was calculated as median 12840 (8800-1731) and neutrophil count was 8450 (4220-12685) cells/mm³. CRP was evaluated in 53 patients; the median was 33.2 (5.32-151) mg/L. Plasma endocan levels were positively correlated with WBC and neutrophil but not correlated with CRP (respectively $p=0.01$ $r = 0.434$, $p = 0.01$ $r = 0.340$, $p = 0.804$ $r = - 0.035$).

In this study, the ROC analysis was evaluated to determine the diagnostic role of endocan in the diagnosis of patients with pneumonia and endocan levels remained below acceptable limits (AUC = 0,547). Based on the ROC curve, an optimal cut-off value for pneumonia diagnosis was set at 1.626 ng / ml of endocan. The positive predictive value was calculated as 92.3% and the negative predictive value as 56.8%. When the plasma endocan levels on the first day of the patient group and plasma endocan levels of the control group were evaluated, sensitivity and specificity were found as 22.64% and 98.18% for pneumonia (Figure 1).

Discussion:

In our study, there was no statistically significant difference between the serum endocan levels of the patient and control groups. The study also did not find a meaningful result when we compared serum endocan levels of hospitalized patients and outpatient groups. Our study showed that endocan is not consistent in determining hospitalization according to the Infectious Diseases Society of America (IDSA). There are very few studies in the related literature on this subject to evaluate the relationship between serum endocan levels and CAP in children. However, a different aspect, of our study from other studies, was that we compared the serum endocan level of hospitalized patients with outpatients. There was no statistical difference in serum endocan levels between the first day and

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fourth day in patients with CAP. According to our study results, endocan was not considered appropriate in the evaluation of the treatment response. However, there were groups of patients (culture positive, requiring MV, and those who died) whose serum endocan levels did not decrease despite treatment. Their results were not statistically significant because of the number of these patients, but their serum endocan levels were higher than control groups. Patients with elevated serum endocan levels need to be more carefully monitored. Further investigation is needed for this subject.

There are few studies in literature evaluating the relationship between pneumonia and endocan. In the study performed by Paketci et al., the serum endocan levels of children with pneumonia were found to be statistically higher than those of the control group¹⁰. The results of our study were not consistent with these studies. In our study, we could say 6 patients had severe pneumonia because of MV needs but Paketici et al. had 29 severe pneumonia patients in their study. For this reason, there may be a difference between that study and our study. Severe pneumonia criteria of the British Thoracic Society (BTS) includes more severe clinical findings than those of the IDSA hospitalization criteria^{11,4}. In our study, patients, who needed MV, had higher serum endocan levels than other patients. These findings suggest that high serum endocan levels are associated with pneumonia severity but we have not been able to identify a relationship with hospitalization. In a study conducted by Kao et al. with adult pneumonia patients. Serum endocan levels were found to be higher than in the control group¹². This discrepancy may have been due to the higher than average age, co-morbidity, or more severe pneumonia of their patients than in our study.

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There are more than pneumonia studies with serum endocan levels. Endocan has been shown to be an important and potent marker of organ failure and mortality in sepsis. In studies investigating better ways to determine the clinical course of sepsis, endocan levels were found to be high in sepsis patients. In addition, high endocan levels were found to be associated with disease severity in terms of shock development and mortality¹³. In a study by Saldır et al. in septic newborns, endocan and IL-6 levels were higher than in non-septic patients. It has been suggested that this is a landmark study for the early recognition of septic newborns and for their differentiation from nonseptic infants¹⁴. When these studies are evaluated, it is understood that the median serum endocan level is increased in infective cases and related with the severity of the disease. In our study, microorganisms were detected in the blood cultures of 6 patients. The median serum endocan levels of these 6 patients were 0.755 (0.190-2.484) ng / ml and 0.523 (0.192-2.898) ng / ml in blood culture negative patients. Although the median serum endocan level was high at the time of diagnosis of the culture positive patients, it was not statistically significant ($p = 0.902$). In the study of Seo et al.¹⁵, serum endocan levels in bacterial patients were shown to be higher in bacteremic patients than in non-bacteremic patients and no correlation was found between serum endocan levels, CRP or PCT. In our study, endocan level was not correlated with CRP level, but was correlated with WBC and neutrophils. The results of our study are similar to those of Seo et al. Endothelial cells form a multifunctional cell lining, that covers the entire inner surface of blood vessels, and they regulate several important physiological and pathological reactions¹⁶. We know that endocan is secreted by endothelial cells in response to proinflammatory cytokines, lipopolysaccharide (LPS), and angiogenic factors. These studies showed

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that if infection is unrestricted and spreads, endothelial cells become activated and the level of serum endocan is increased¹⁷. This may be a sign that the prognosis of the disease will worsen.

In our study, ROC analysis was evaluated to determine the diagnostic role of endocan in the diagnosis of patients with pneumonia. Endocan levels remained below acceptable limits (AUC = 0.547). In the study performed by Petekci. et al. the endocan level AUC (0.769) value was not found to be significant for pneumonia, similar to our study¹⁰. These results might not be hopeful because sensitivity and specificity of endocan is not found to be higher when compared to old and new markers such as CRP, PCT, and copeptin, as mentioned in a recently published meta-analysis¹⁸. A limitation of our study is the fact that the number of patients was low and we did not discriminate between viral and bacterial pneumonia. In addition, patients could be grouped according to disease severity score.

According to the results of our study, endocan had no significant value in determining patients' hospitalization. However, high serum endocrine levels may be significant in determining the severity of the disease and poor prognosis. Further investigations are needed to inspect the effects of endocan on CAP.

Author Contributions

Hangul M. interpreted the results, drafted the manuscript, and executed the statistical analyses. He reviewed the literature, wrote the final version of the article, revised the manuscript, and approved the final version of the manuscript. Kose M. designed the study and constructed a hypothesis for research. He contributed to the interpretation of results, revised the manuscript, and approved the final version of the manuscript. Ozturk D. took responsibility in execution of the experiments, patient

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follow-up, data management, reports, revised the manuscript, and approved the final version of the manuscript. Ketı D. performed the laboratory assays, reviewed the manuscript, and approved the final version of the manuscript

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Table 1: Demographic data of patient and control groups.

		Patients n (%)	Control group n(%)
Gender	Male	31 (58.5%)	29 (52.7%)
	Female	22 (41.5%)	26 (47.3%)
Age (mounth)	Mean (minimum-maximum)	52 (7- 192)	56(5- 192)
First day Serum Endocan level (ng/ml) (median)		0.52(0.19- 2.98)*	0.54 (0.18-1.77)*

No statistically significant difference was determined between the CAP and control groups in respect of age and gender. $p>0,05$, *there was not statistically significant difference between first day serum endocan level the CAP and control groups

Table 2: Clinical features of patient group and comparison of the endocan levels

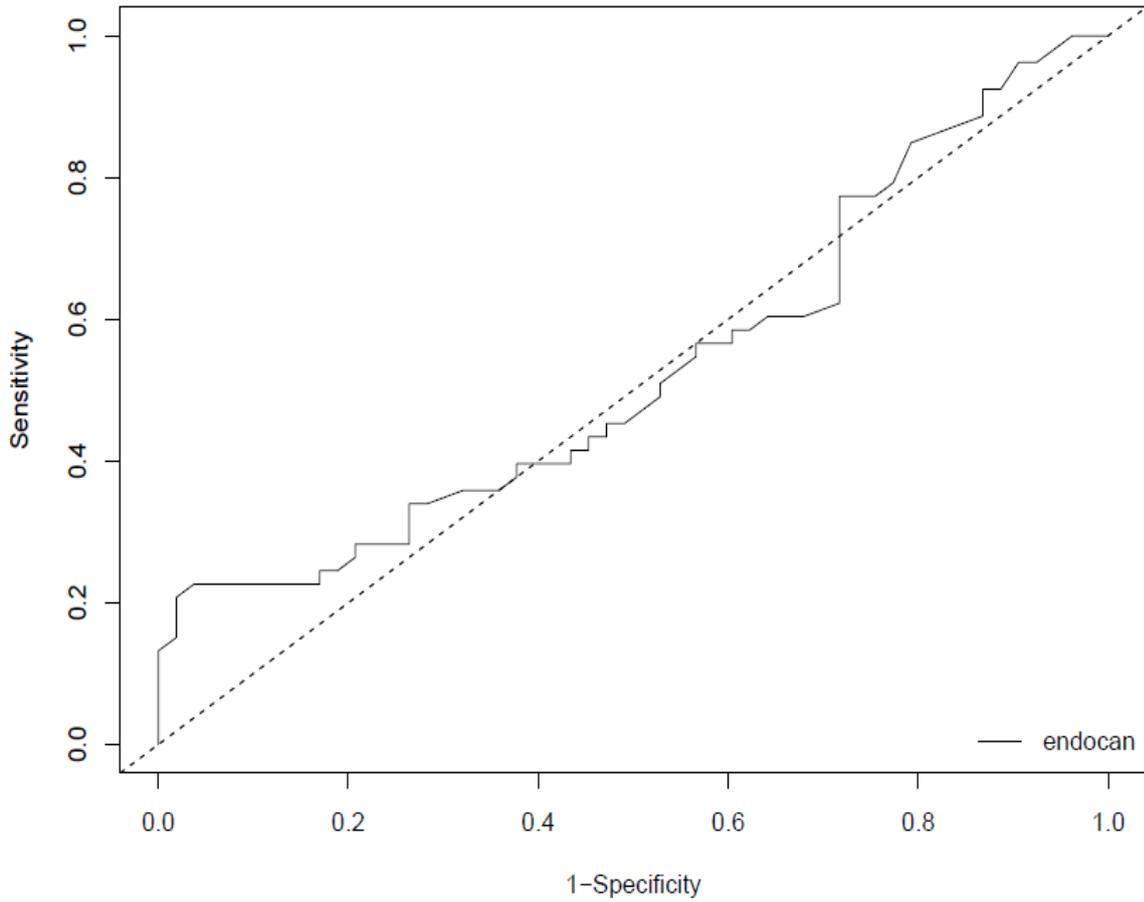
Endocan level of patient gruops; Median (min-max) (ng/ml)		First day	4th day	p
		0.52(0.19- 2.98)	0.52 (0.17- 2.47)	>0.05
Follow-up n(%)	Outpatiens 15, (28.4%)	0,66 (0.35-1.69)	0.58 (0.34- 1.77)	>0.05
	Hospitalization 38, 71.6(%)	0.43 (0.28-1.06)	0.41 (0.29- 1.13)	>0.05
Complication n (%)	No-Complication 35, (66%)	0.55 (0.19- 2.98)	0.49 (0.17- 2.47)	>0.05
	Complication 15, (28.3%)	0.34 (0.20- 2.66)	0.39 (0.19- 2.28)	>0.05

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	Dead patients 3, (5.7%)	0.32 (0.19-0.41)	0.71 (0.68-1.96)	>0.05
Mechanical ventilation (MV) n(%)	Non- MV 47, (88.7%)	0.52 (0.19-2.98)	0.43 (0.17-2.47)	>0.05
	MV 6, (11.3%)	0.80 (0.19-2.65)	1.58 (0.68-1.96)	
Culture	Positive 6, (11.3%)	0.75 (0.19-2.48)	1.62 (0.29-2.28)	>0.05
	Negative 47, (88.7%)	0.52 (0.19-2.89)	0.48 (0.17-2.47)	

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Figure 1: ROC analyses of endocan, in patients with cap



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