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Can Serum Endocan Levels be Used as an Early Prognostic Marker for Endothelial Dysfunction in COVID-19?

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Abstract

In this study, we aimed to investigate whether degree of pneumonia and COVID-19 prognosis are associated with serum endocan levels at the early stage, when vascular damage has started. Patients between the ages of 18–85 years who were hospitalized and followed up with a diagnosis of COVID-19 were included in the study. A total of 80 patients were divided into 2 groups as mild/moderate pneumonia and severe pneumonia. Serum endocan levels were measured on the 8th day from the onset of symptoms in all patients. Of the 80 patients included in the study, 56.3% were female and 43.8% were male. There was no significant relationship between serum endocan levels and degree of pneumonia ($P = .220$) and prognosis of the disease ($P = .761$). The correlation analysis indicated a weak positive correlation between serum endocan levels and lactate level in venous blood gas ($r = .270$; $P = .037$). During the 28-day follow-up, the mortality rate was 3.75%. It was determined that the serum endocan levels was not associated with the degree of pneumonia and was not an early prognostic marker for COVID-19.

Keywords

COVID-19, SARS-CoV-2, endocan, endothelial dysfunction

Introduction

COVID-19 is a multisystemic disease that first appeared in China in December 2019 and since then, has spread all over the world.[1] Classical symptoms of the disease include fever, weakness, dry cough, and shortness of breath; acute respiratory distress syndrome (ARDS), cardiovascular, thrombotic, and embolic events can be seen in the severe course of the disease.[2,3] These findings support the presence of vascular endothelial damage and thromboinflammation. Currently, there are no non-invasive examinations that can reveal the damage and inflammation in the endothelial tissue in the early period. Early detection of endothelial damage will provide timely premedication advantage and will contribute to a favorable prognosis. One of the parameters that can indicate endothelial tissue damage non-invasively is endocan.

Endocan (endothelial specific molecule-1, ESM-1), which is a free circulating proteoglycan produced from endothelial cells, is responsible for immunity, inflammation, and endothelial function.[4,5] Endocan levels were reported to increase in various diseases related to endothelial dysfunction such as hypertension, cardiovascular disease, sepsis, and ARDS.[6-9] Endothelial dysfunction was also reported in COVID-19.[10,11] However, the number of studies on endothelial dysfunction and endocan levels in COVID-19 is limited.

Therefore, in this study, we planned to investigate whether the serum endocan is associated with the degree of pneumonia and the prognosis in COVID-19.

Methods

Study Population

This prospective and cross-sectional study was conducted between September 1, 2020 and December 1, 2020 at the Internal Medicine Clinic of the Health Sciences University Ankara City Hospital.

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Patients between the ages of 18–85 years that were hospitalized and followed up with a diagnosis of COVID-19, which was confirmed by the RT-PCR test, were included in the study. Patients were divided into 2 groups as mild/moderate pneumonia and severe pneumonia according to COVID-19 Diagnosis Guide of the Turkish Ministry of Health.[12] The study included a total of 80 patients, with 40 patients in each group. In addition to routine tests, blood samples were taken from the patients for serum endocan level analysis. At the time of blood draw, all patients were on the 8th day of symptom onset. In patients that received pulse steroid therapy during their hospital stay, blood samples were taken before initiation of this therapy.

The exclusion criteria were pregnancy, active smoking, chronic restrictive and obstructive pulmonary disease, acute/chronic renal failure, acute/chronic hepatic failure, malignancy, rheumatologic disease, receiving immunosuppressive therapy, recent acute myocardial infarction, history of cerebrovascular events or peripheral artery disease, alcohol and substance abuse, dementia, Parkinson's disease, and unconfirmed diagnosis of COVID-19.

Mild/moderate pneumonia was defined as having respiratory rate <30/min, room air oxygen saturation (SpO2) >90%, and mild/moderate pneumonia findings on chest radiography or tomography. Severe pneumonia was defined as having tachypnea (≥30/min), SpO2 level ≤90% in room air, and bilateral diffuse pneumonia findings on chest radiography or tomography.

The demographic (age and gender), clinical (symptoms and outcomes) characteristics, and laboratory findings of the patients were recorded from the patient files. Radiological evaluation included radiography and computed tomography.

Ethics committee approval was obtained from Ankara City Hospital Ethics Committee (approval number: E1/1154/2020). Written and verbal consents were obtained from all patients or relatives included in the study.

Biochemical Analyses

The blood samples were collected for each participant in the morning after an overnight fast of at least 8 h. Blood was collected into a tube containing ethylenediamine tetraacetic acid for whole blood analysis. Biochemical parameters (glucose, urea, creatinine, sodium, potassium, alanine transaminase, aspartate transaminase, ferritin, fibrinogen, interleukin-6 (IL-6), c-reactive protein (CRP), and procalcitonin) were measured using standard laboratory techniques.

For endocan level measurements, blood samples were allowed to coagulate for 30 min in room air, and then serum and plasma levels were separated by centrifugation at 1700 g for 10 min. Serum samples were kept at −80°C until the day of analysis. After the sample collection was completed, the serum endocan level was measured in the same laboratory by the same technician.

Serum Endocan Level Measurement

Endocan level measurements were carried out by using Human ESM1/Endocan Elisa (SinoGeneClon Biotech Co. Ltd, Hangzhou, China; Catalog Number: SG-10619, LOT number: 202009) 96-test kit in accordance with the manufacturer's instructions. Sensitivity of the endocan kit was .6 pg/ml, the intra-assay coefficient of variation (CV) was <8% while inter-assay CV was <10%. The measurable range was 3.5–200 pg/ml.

COVID-19 RT-PCR

Samples were taken from the upper respiratory tract (nose and throat) with a swab or sputum. SARS-CoV-2 RNA detection was made in the Clinical Microbiology Laboratory at the Ankara City Hospital by using Bio Speedy Bioeksen COVID-19 RT-qPCR diagnostic kit (Istanbul, Turkey) and Coronex COVID-19 RT-qPCR diagnostic kit (Ankara, Turkey).

Statistical Analyses

Statistical evaluation was performed using the Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, IL) program. The normality of data distribution was evaluated by Kolmogorov–Smirnov test. Normally distributed numerical variables were expressed as mean ± standard deviation, while numerical variables not showing normal distribution were expressed as median (quartiles 25–75). Categorical variables were expressed as numbers and percentages. Chi-Square and Fisher's exact test were used in comparison of categorical data. Student's t-test was used to compare normally distributed numerical variables according to the severity of pneumonia, and the Mann–Whitney U test was used to compare numerical variables that did not show a normal distribution. The distribution of the endocan levels among 2 groups was evaluated with the Kruskal–Wallis H test. The relationship between endocan levels and numerical variables was examined using Spearman Correlation Analysis. In statistical analysis, confidence interval (CI) was 95% and significance as 2 tailed $P < .05$.

Results

Eighty patients were included in the study. Forty patients were in the mild/moderate pneumonia group, and 40 patients were in the severe pneumonia group. Female gender (56.3%) was more common in the entire study population, but there was no significant difference between the 2 groups ($P = .071$). The mean age of the patients participating in the study was 57.8 years (Table 1). RT-PCR test results were positive in all patients.

The clinical findings of the patients are detailed in Table 2. While 22.5% (n = 18) of the patients received oxygen therapy with high flow/reservoir mask, the rate of those who received total oxygen therapy was 50% (n = 40). All patients who received oxygen therapy were in the severe pneumonia group. Common symptoms were weakness, loss of appetite, cough, fever, and shortness of breath, while less commonly observed

Table 1. Demographic Characteristics According to the Severity of Pneumonia.

Variables	Entire population n = 80	Severity of pneumonia		p
		Mild-moderate n = 40	Severe n = 40	
Age (Years)	57.8 ± 14.3	55.4 ± 14.3	60.1 ± 14	.140
Gender, n (%)				
Female	45 (56.3)	18 (45.0)	27 (67.5)	.071
Male	35 (43.8)	22 (55.0)	13 (32.5)	
Comorbid diseases, n (%)				
Hypertension	40 (50.0)	17 (42.5)	23 (57.5)	.263
Diabetes mellitus	31 (38.8)	11 (27.5)	20 (50.0)	.066
Coronary artery disease	16 (20.0)	6 (15.0)	10 (25.0)	.402
Thyroid disease	7 (8.8)	3 (7.5)	4 (10.0)	.999
Heart failure	4 (5.0)	1 (2.5)	3 (7.5)	.608
Malignancy	–	–	–	–
Chronic renal failure		–	–	–
Rheumatological disease	–	–	–	–

Numerical variables are shown as mean ± standard deviation and median (25–75 quartiles).
Categorical variables were shown as number (%).
$P < .05$ shows statistical significance.

Table 2. Distribution of Clinical Findings According to the Severity of Pneumonia.

Variables	Entire population n = 80	Severity of pneumonia		p
		Mild-moderate n = 40	Severe n = 40	
Fever (°C)	36.7 ± 0.6	36.5 ± 0.5	36.8 ± 0.7	.024*
SBP, mmHg	118.1 ± 13.9	120 ± 14.4	116.3 ± 13.4	.241
DBP, mmHg	69.8 ± 8.9	70.8 ± 9.7	68.9 ± 8	.330
Pulse, beats/min	81.7 ± 11.2	81.8 ± 9.9	81.7 ± 12.5	.961
Saturation, %	90.6 ± 4.8	94.7 ± 2	86.5 ± 2.9	<.001*
High flow-reservoir mask, n (%)				
Absent	62 (77.5)	40 (100.0)	22 (55.0)	<.001*
Present	18 (22.5)	0 (.0)	18 (45.0)	
Oxygen therapy, n (%)				
Absent	40 (50.0)	40 (100.0)	–	<.001*
Present	40 (50.0)	–	40 (100.0)	
Symptoms, n (%)				
Weakness, loss of appetite	78 (97.5)	39 (97.5)	39 (97.5)	.999
Cough	58 (72.5)	24 (60.0)	34 (85.0)	.023*
Fever	52 (65.0)	26 (65.0)	26 (65.0)	.999
Shortness of breath	44 (55.0)	11 (27.5)	33 (82.5)	<.001*
Chest pain	13 (16.3)	4 (10.0)	9 (22.5)	.225
Diarrhea	14 (17.5)	7 (17.5)	7 (17.5)	.999
Loss of taste/smell	4 (5.0)	3 (7.5)	1 (2.5)	.608
Symptom duration, day	8	8	8	.999

Numerical variables are shown as mean ± standard deviation and median (25–75 quartiles).
Categorical variables were shown as number (%).
$P < .05$ shows statistical significance.
Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure.

symptoms were chest pain, diarrhea, and loss of taste/smell. All patients were on the 8th day of symptom onset when blood samples were collected for serum endocan level measurements. The rate of patients with cough (85% and 60%, respectively; $P = .023$) and shortness of breath symptoms (82.5% and 27.5%, respectively; $P < .001$) was higher in patients with severe pneumonia compared with those with mild/moderate pneumonia. The distribution of other

Table 3. Distribution of Treatment and Prognosis According to the Severity of Pneumonia.

Variables	Entire population n = 80	Severity of pneumonia		p
		Mild-moderate n = 40	Severe n = 40	
Treatment, n (%)				
Favipravir	80 (100.0)	40 (100.0)	40 (100.0)	–
Enoxaparin	79 (98.8)	40 (100.0)	39 (97.5)	.999
Antibiotic	68 (85.0)	30 (75.0)	38 (95.0)	.025*
Hydroxychloroquine	52 (65.0)	25 (62.5)	27 (67.5)	.815
Prednol	46 (57.5)	12 (30.0)	34 (85.0)	<.001*
Colchicine	20 (25.0)	8 (20.0)	12 (30.0)	.439
Pulse steroid	11 (13.75)	0 (0)	11 (27.5)	<.001*
Dipyridamole	6 (7.5)	2 (5.0)	4 (10.0)	.671
Hospitalization, days	9 (3-30)	7.5 (3-21)	12 (4-30)	<.001*
28-day survival, n (%)				
Dead	3 (3.75)	0 (0)	3 (7.5)	.077
Alive	77 (96.25)	40 (100.0)	37 (92.5)	

Numerical variables are shown as mean ± standard deviation and median (25–75 quartiles).
Categorical variables were shown as number (%).
$P < .05$ shows statistical significance.

symptoms did not differ significantly according to the severity of pneumonia (Table 2).

The mean hospitalization time of the patients was 9 days. The mean length of hospitalization (12 vs 7.5, $P < .001$) and mortality rate (7.5 vs 0%, $P = .077$) were higher for patients with severe pneumonia compared with those with mild/moderate pneumonia (Table 3). During the 28-day follow-up, the mortality rate was 3.75% (n = 3). No significant relationship was found between endocan levels and 28-day survival ($P = .761$).

The endocan level did not differ significantly in patients with severe pneumonia compared with those with mild/moderate pneumonia (264.8 vs 311.2 pg/ml, respectively; $P = .220$). Patients with severe pneumonia had lower lymphocyte levels ($P = .008$) and higher neutrophil, fibrinogen, IL-6, ferritin, and CRP levels ($P < .001$ for all) compared with those with mild/moderate pneumonia (Table 4).

A weak positive correlation was found between the endocan and lactate levels in venous blood gas (r = .270; $P = .037$). No correlation was found between endocan levels and lymphocyte, CRP, fibrinogen, IL-6, procalcitonin, and ferritin (r = .118, $P = .279$; r = −.186, $P = .099$; r = −.124, $P = .271$; r = −.178, $P = .220$; r = .003, $P = .977$; r = −.116, and $P = .306$, respectively).

Discussion

In this study, we examined the relationship between the clinical course of COVID-19 and serum endocan level. We found that the serum endocan levels measured from samples obtained on the 8th day after the onset of symptoms were not closely related to the prognosis of the disease in patients with mild/moderate pneumonia and severe pneumonia. Moreover, no correlation was found between endocan levels and CRP, procalcitonin, IL-6, fibrinogen, and ferritin. However, a weak positive correlation was found between the endocan levels and the lactate level in venous blood gas.

Endothelial dysfunction was first described in 1990 by Panza et al. in the hypertensive patient group.[13] It can also be associated with type 1 diabetes mellitus, type 2 diabetes mellitus, coronary artery disease, congestive heart failure, chronic kidney disease, dyslipidemia, obesity, ischemic stroke, hyperhomocysteinemia, sepsis, sedentary life, and smoking.[14-25] Various imaging methods and biochemical biomarkers, including serum endocan, are used to detect endothelial dysfunction.[26] Serum endocan levels have been reported to increase in diseases with endothelial dysfunction.[6-9]

Morbidity and mortality in COVID-19 infection can be explained by the destruction of the endothelial tissue, thromboinflammation, and emboli that develop after thromboinflammation.[27] According to the SARS-CoV-2 pathogenesis hypothesis proposed by Lin et al.,[28] the first 7 days of the disease can be considered as the viremia phase, after which the acute (pneumonia) phase develops. Based on this hypothesis, we measured the serum endocan levels on day 8 of symptom onset, which we considered as the early stage of vascular damage. This is one of the strengths of our study, since other studies have not specified the duration of symptoms.

There are limited studies examining relationship between COVID-19 and endocan levels. In Medetalibeyoglu et al.'s study, elevated serum endocan levels were associated with poor prognosis in COVID-19. Their study was retrospective, and serum endocan levels were analyzed within the first 24 h of hospital admission.[29]

In Gorgun et al.'s study, serum endocan levels of patients hospitalized in the service or intensive care unit due to

Table 4. Laboratory Findings According to the Severity of Pneumonia.

Variables	Entire population n = 80	Severity of pneumonia		p
		Mild-moderate n = 40	Severe n = 40	
Glucose (mg/dL)	107	94 (66-393)	115.5 (80-461)	.013*
Urea (mg/dL)	40.5	34 (14-79)	51 (23-88)	.002*
Creatinine (mg/dL)	1 ± .3	.9 ± .3	1 ± .3	.022*
Sodium(mEq/L)	138.2 ± 3.8	139.2 ± 2.6	137.1 ± 4.5	.015*
Potassium (mEq/L)	4.2 ± .5	4.3 ± .5	4.2 ± .6	.583
ALT (U/L)	33	32.5 (8-184)	33 (12-324)	.912
AST (U/L)	40	36 (9-131)	40 (14-95)	.117
Leukocytes ($x10^9$/L)	7.37	6.17 (2.7-15.8)	8.38 (3.34-18.5)	.003*
Neutrophils ($x10^9$/L)	5.01	3.79 (1.8-14.6)	6.6 (1.98-16.3)	<.001*
Lymphocytes ($x10^9$/L)	1.09	1.39 (.45-3.62)	.905 (3.3-3.64)	.008*
Hemoglobin (g/dL)	12.9 ± 1.7	13 ± 1.9	12.8 ± 1.5	.622
MCV (fL)	86.6 ± 6	87.5 ± 7	85.8 ± 4.8	.205
Thrombocytes ($x10^9$/L)	261	232.5 (115-605)	280 (110-687)	.213
INR	1.1 ± .3	1.1 ± .3	1.1 ± .3	.437
Fibrinogen (g/L)	4.9 ± 1.6	4.2 ± 1.4	5.6 ± 1.6	<.001*
IL-6 (pg/ml)	33.9	13.4 (1.8-86)	49.1 (4.2-130)	.001*
Ferritin (μg/L)	278.5	179.5 (13-1540)	372.5 (66.7-1579)	<.001*
ESR (mm/hour)	39	25 (3-99)	45 (3-116)	.067
CRP (mg/L)	37	13 (.5-152)	56 (.8-347)	<.001*
Procalcitonin (μg/L)	.05	.03 (.02-1.06)	.08 (.02-2.81)	.003*
Endocan (pg/ml)	297.6	311.2 (135-878.7)	264.8 (150-3778.2)	.220

Numerical variables are shown as mean ± standard deviation and median (25–75 quartiles).
Categorical variables were shown as number (%).
$P < .05$ shows statistical significance.; Abbreviations: ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, INR: International normalized ratio, IL-6: Interleukin-6, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, MCV: Mean corpuscular volume.

COVID-19 were significantly higher compared with those of healthy controls. They measured serum endocan levels by adding biotinylated human endocan antibodies to samples. While their mean serum endocan level was 243.5 ng/mL in the patient group, it was 201.5 ng/mL in the control group.[30] Differences in measurement methods may be the reason why their results are different from ours.

In the study of Pascreau et al., patients were divided into groups as non-ARDS, mild/moderate ARDS, and severe ARDS according to the Berlin definition,[31] and endocan and cathepsin-G-bound endocan levels were measured at admission and during hospitalization. In the mild/moderate ARDS group, endocan levels were higher on day 3–4 and day 5–6 compared with day 1–2, but no such increase was observed in the severe ARDS group. It was thought that the decrease in endocan levels in the severe ARDS group during the hospitalization period and low endocan levels during sepsis may predict worsening of ARDS.[32]

In our study, ROC curve analysis with endocan levels was performed to predict mortality. However, the number of patients with mortal outcomes (n = 3) was low, and no significant results were obtained (AUC: .552). In Medatalibeyoğlu et al.'s study, the serum endocan level of 276.4 ng/mL has been shown to indicate poor prognosis with 97% sensitivity and 85% specificity.[29] Gorgun et al.[30] reported that endocan level of 202 ng/mL in serum samples taken at the time of admission had a sensitivity of 86.7% and a specificity of 50% for indicating poor COVID-19 prognosis.

The small number of patients and the cross-sectional design are the biggest limitations of our study. Since it was a cross-sectional study, the variation of the endocan level based on the treatment and the clinical follow-up of the patient could not be determined. In addition, our patients had some of the comorbid conditions affecting the endocan levels (hypertension, diabetes mellitus, coronary artery disease, and heart failure), and their basal endocan levels were unknown. Other limitations include not knowing whether there is an underlying malignancy that we were not aware of and not using additional biochemical markers such as asymmetric dimethylarginine, pentraxin-3, or imaging methods to show endothelial damage.

The strengths of the study are prospective design, same duration of symptoms in both groups, and the inclusion of 28-day survival data.

In conclusion, we found that the endocan levels in the blood samples obtained on the 8th day from the onset of COVID-19 symptoms did not show a significant difference in groups classified according to clinical outcome and were not associated with prognosis in either group. However, due to the

aforementioned limitations, there is a need for comprehensive, prospective, randomized controlled studies that will include larger patient populations, evaluate endothelial dysfunction with additional methods, and repeat these investigations at different stages of the disease.

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Author's Note

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Declaration of Conflicting Interests

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