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Serum Endocan Levels as a Valuable Biomarker for Discrimination of Critical and Stable COVID-19 Patients

Kritik ve Stabil COVID-19 Hastalarının Ayırımı için Değerli Bir Biyobelirteç Olarak Serum Endokan Düzeyleri

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Abstract

Objective: The primary aim of the study was to investigate the relationship between serum endocan levels and clinical condition of Coronavirus disease-2019 (COVID-19) patients. The secondary aim was to investigate the associations between the serum endocan levels and other inflammatory parameters with regard to clinical outcomes.

Method: A total of 80 COVID-19 patients, 44 in stable and 36 in critical condition, with positive polymerase chain reaction test result, older than 18 years of age and whose first admission complaint was not either heart attack or ischemic stroke were included in this study. Patients' characteristics and clinical outcome, hematological and biochemical parameters, thorax computed tomography, treatment approach, vital signs, and COVID-19 symptoms were analyzed.

Results: The mean age of the critical patients was significantly higher than that of the stable patients (71.00±13.27 and 53.36±17.80; p<0.001). Blood and serum parameters (C-reactive protein, ferritin, procalcitonin, lactate, neutrophil-to-lymphocyte ratio, D-dimer, troponin T, urea, creatinine, white blood cell, and international normalized ratio) were significantly higher in critical patients (p<0.05). Serum endocan levels were significantly higher in critical patients (518.9±513.31 ng/mL; p<0.001). Endocan, age, lactate, and troponin T were found to be significantly effective to distinguish critical patients from the stable patients in the multivariate model. Receiver operating characteristic curve analysis revealed that 244.9 ng/mL endocan level had 88.9% sensitivity and 63.6% specificity for critical patients.

Öz

Amaç: Çalışmada primer amaç, Koronavirüs hastalığı-2019 (COVID-19) hastalarında serum endokan düzeyleri ile klinik durumları arasındaki ilişkiyi değerlendirmekti. Sekonder olarak ise klinik sonuçlar açısından serum endokan seviyeleri ile diğer enflamatuvar parametreler arasındaki ilişkileri ortaya koymayı hedefledik.

Yöntem: Çalışmaya, polimeraz zincir reaksiyon testi pozitif olan, 18 yaşından büyük, 44'ü stabil, 36'sı kritik durumda, ilk başvuru şikayeti kalp krizi veya iskemik inme olmayan toplam 80 COVID-19 hastası dahil edildi. Hastaların özellikleri ve klinik sonuçları, hematolojik ve biyokimyasal parametreleri, endokan düzeyleri, toraks bilgisayarlı tomografileri, tedavi yaklaşımları, vital bulguları ve COVID-19 semptomları değerlendirildi.

Bulgular: Kritik hastaların ortalama yaşı stabil hastalardan anlamlı derecede yüksekti (71,00±13,27 ve 53,36±17,80; p<0,001). Kritik hastalarda kan ve serum parametreleri (C-reaktif protein, ferritin, prokalsitonin, laktat, nötrofil-lenfosit oranı, D-dimer, troponin T, üre, kreatinin, beyaz kan hücresi ve uluslararası normalleştirilmiş oran) anlamlı olarak daha yüksekti (p<0,05). Kritik hastalarda serum endokan düzeyleri anlamlı olarak yüksekti (518,9±513.31 ng/mL; p<0,001). Endokan, yaş, laktat ve troponin T'nin kritik hastaları stabil hastalardan ayırt etmede önemli ölçüde etkili olduğu bulundu. Kritik hastalar için 244,9 ng/mL endocan seviyesinin %88,9 duyarlılığa ve %63,6 özgüllüğe sahip olduğu görüldü.

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Abstract

Conclusion: Serum endocan levels are a useful biomarker to predict the clinical condition on the admission and may predict the prognosis and outcomes of COVID-19 patients.

Keywords: COVID-19, endocan, prognosis

Öz

Sonuç: Serum endokan seviyeleri, başvurudaki klinik durumu tahmin etmek için yararlı bir biyobelirteçtir ve COVID-19 hastalarının prognozunu ve sonuçlarını öngörebilir.

Anahtar kelimeler: COVID-19, endokan, prognoz

Introduction

Coronavirus disease-2019 (COVID-19) that emerged from China is a multisystem disease (1). Various symptoms fewer, dyspnea, fatigue, headache, loss of smell and taste were reported for COVID-19 (2-5), however, the complete list of manifestations of COVID-19 is yet to be clarified. In addition, other COVID-19 symptoms such as cardiovascular events ranging from arrythmias to sudden death in patients with or without an accompanying cardiovascular disease (6,7). Moreover, coagulopathy has been reported in approximately 50% of severe COVID-19 patients (8).

A serious effort has been made in the diagnosis and classification disease severity in COVID-19. For this purpose, various studies have investigated the possible biomarkers and associations between them, COVID-19 severity, and outcome (9-11). Serum endothelial-specific molecule-1 (endocan) is a proteoglycan that has been implicated as a marker of endothelial cell damage (12,13) and was found that its secretion is induced by pro-inflammatory cytokines, lipopolysaccharides (14) and pro-angiogenic factors (15). Several studies reported that serum endocan levels were elevated in various endothelium-related pathologies including diabetes (16), coronary artery disease (17), hypertension (18) and pulmonary thromboembolism (19,20).

Serum endocan levels were associated with the mortality in patients with coagulopathy and mortality in patients with disseminated intravascular coagulation (21). In addition, endocan levels were indicated to be a potential inflammatory and cardiovascular disease marker (12). On the other hand, in COVID-19 patients, endocan was reported to be useful prognostic biomarker (7,22). Therefore, in this study, the primary aim was to investigate the serum endocan levels in COVID-19 patients according to their clinical condition with regards to mortality and morbidity. The secondary aim of the study was to investigate the associations between the serum endocan levels and other inflammatory parameters with regards to clinical outcome.

Materials and Methods

Study Design and Population

This prospective single-centered study was conducted between 01/01/2021 and 31/12/2021 after the approval by Clinical Research Ethics Committee of University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital (date: 22.12.2020, number: 1753). All procedures performed were in line with the ethical standards of the Institutional and/or National Research Committee and with the 1964 Helsinki Declaration and its later amendments.

A total of 80 COVID-19 patients, 44 of them were stable and 36 of them were critical, were included in the study. The patients admitted to our hospital serving as a pandemic hospital and whose COVID-19 polymerase chain reaction (PCR) test result were detected positive in the emergency department (ED), patients older than 18 years of age and patients whose first admission complaint was not either heart attack or ischemic stroke were included in this study. The exclusion criteria were being younger than 18 years of age, having negative PCR test result, having missing data in the patient files, and having the first admission complaint as either heart attack or ischemic stroke. Written informed consents of the patients were obtained on arrival to the hospital for their anonymized information to be published.

Patients' clinical outcomes were recorded as discharge, hospitalization in ward, referral to intensive care unit (ICU), and death. Hematological and biochemical parameters, thorax computed tomography (CT), treatment that they received, vital signs, COVID-19 symptoms and chronic disease were investigated and compared between the patient groups who were in stable condition and who were in critical condition.

Intensive Care Admission Criteria

- Patients whose vitals are unstable:

- Dyspneic and tachypneic patients (respiratory rate ≥30/min)
- SpO_2 <90% or PaO_2 <70 mmHg despite 5 L/min oxygen therapy

- Tachycardia >100/min
- Hypotension (systolic blood pressure <90 mmHg and more than 40 mmHg decrease from normal systolic blood pressure (SBP) and mean arterial pressure <65 mmHg

- Clinical and laboratory abnormality:

- Increased oxygen requirement in follow-ups
- Patients with acute kidney injury, acute liver function tests, confusion, acute organ dysfunction such as acute bleeding diathesis and immunosuppression
- Troponin elevation and arrhythmia
- In arterial blood gas: Lactate >2 mmol and PaO_2/FiO_2 <200
- Presence of skin disorders such as skin findings of capillary return disorder

Measurement of Serum Endocan Levels

Serum endocan levels were measured by using Human Endothelial cell-specific molecule 1 (Endocan) Enzyme-Linked ImmunoSorbent Assay (ELISA) Kit (E3160Hu; Bioassay Technology Laboratory) according to manufacturer's instruction. Basically, whole blood samples collected were incubated at room temperature for 20 minutes and centrifuged at 3000 rpm for 20 minutes. The serum samples collected were aliquoted and stored at -80 °C until the analyses. Serum endocan levels were determined by measuring absorbance of the samples on a microplate reader at 450 nm by using a microplate reader (ELx800 Absorbance Microplate Reader (BioTek Instruments).

Statistical Analysis

Statistical analyses were conducted by using SPSS version 22.0 (IBM, USA). In descriptive statistics, mean, standard deviation, median, frequency, and ratio were used. Kolmogorov-Smirnov test was used to evaluate the distribution of the data. Quantitative independent data were analysed by using either unpaired t-test or Mann-Whitney U test depending on the distribution of the data. Qualitative independent data were analysed by using the chi-square test in case of the test conditions were met, or else Fischer's Exact test was used. Univariate or multivariate logistic regression analyses were performed to investigate the level of effect. Receiver operating curve ROC analysis was performed to investigate the effect of endocan in predicting the clinical status of the patient. A p-value lower than 0.05 was considered as statistically significant.

Results

The mean age of the patients were 61.30±18.11 years, while the mean age of the critical patients was significantly higher than the stable patients (71.00±13.27 vs. 53.36±17.80; p<0.001). On the other hand, there were no significant associations between the gender and the clinical status of the patients (p>0.05). With regards to the symptoms, coughing was more common in stable patients (p=0.020), while general status instability was more common in critical patients (p=0.001). However, there were no associations between the patients' clinical status and the presence of chronic diseases. SBP and diastolic blood pressure was significantly lower, while heart rate (HR) was significantly higher in critical patients (p<0.05). Moreover, body temperature and respiratory rate were significantly higher in critical patients, while oxygen saturation was significantly lower in stable patients (p<0.001; Table 1).

Serum endocan levels were significantly higher in the critical patients than stable patients (p<0.001). On the other hand, while alanine transaminase (ALT) levels did not significantly differ between the groups, all other hematological parameters were significantly higher in critical patients (p<0.05). However, PaO_2/FiO_2 was significantly lower in critical patients (p<0.001; Table 2).

Among the thorax CT infiltrative involvements of the patient groups at the time of admission to the ED, moderate and severe involvements were seen critical group, and advanced involvement was significantly higher in this group than in the stable group (p< 0.001). It was determined that 18 patients in the critically ill group received endotracheal mechanical ventilation therapy. None of the patients in the stable group received mechanical ventilation. Antiviral treatment was given to all patients, while the number of patients receiving anticoagulant, antibiotics, steroid, high-flow O_2 therapy and positive inotropic agents was significantly higher in the critical group than in the stable group (p<0.05). Mortality was observed in 14 patients, and all of these patients were in the critical group (Table 3).

In the univariate model, endocan, age, C-reactive protein, procalcitonin, ferritin, lactate, neutrophil-to-lymphocyte ratio, D-dimer, high-sensitivity troponin T and international normalized ratio levels showed significant effectiveness in distinguishing the critical group from the stable group (p<0.05). On the other hand, it was determined

Table 1. Symptoms, chronic diseases present and vital signs of the patients according to clinical status of the patients

	Critical [n (%)]	Stable [n (%)]	Total [n (%)]	p-value
Gender				
Male	22 (61.1%)	25 (56.8%)	47 (58.8%)	0.873 χ^2
Female	14 (38.9%)	19 (43.2%)	33 (41.2%)	
Age (mean ± SD)	71.0±13.27	53.3±17.79	61.3±18.1	**0.001 t**
Symptoms-chronic diseases				
Fewer	11 (30.6%)	10 (22.7%)	21 (26.3%)	0.592 χ^2
Dyspnea	33 (91.7%)	33 (75.0%)	66 (82.5%)	0.075 χ^2
Cough	13 (36.1%)	22 (50.0%)	35 (43.8%)	0.308 χ^2
Diarrhea	2 (5.5%)	4 (9.1%)	6 (7.5%)	0.685 χ^2
Myalgia	5 (13.9%)	7 (15.9)	12 (15.0%)	0.801 χ^2
Loss of taste/smell	3 (8.3%)	9 (20.5%)	12 (15%)	0.208 χ^2
Sore throat/ headache	1 (2.7%)	9 (20.5%)	10 (12.5%)	**0.020 χ^2**
General status instability	11 (30.6%)	1 (2.2%)	12 (15.0%)	**0.001 χ^2**
CAD	9 (25.0%)	13 (29.5%)	22 (27.5%)	0.840 χ^2
HT	13 (36.1%)	17 (38.6%)	30 (37.5%)	0.816 χ^2
DM	11 (30.6%)	15 (34.1%)	26 (32.5%)	0.924 χ^2
KOAH	5 (13.9%)	4 (9.1%)	9 (11.3%)	0.724 χ^2
Malignancy	4 (11.0%)	3 (6.8%)	7 (8.75%)	0.695 χ^2
CKD	2 (5.5%)	1 (2.2%)	3 (3.75%)	0.585 χ^2
CVE	3 (8.3)	2 (4.5%)	5 (6.3%)	0.653 χ^2
Vital signs (median/min-max)				
SBP (mmHg)	105.0 (7-160)	120.0 (90-160)		**0.001ᴍ**
DBP (mmHg)	70.0 (40-100)	76.0 (60-100)		**0.005ᴍ**
HR (beat per min)	110.0 (90-130)	88.0 (70-115)		**<0.001ᴍ**
Body temperature (°C)	37.6 (36.7-39.0)	36.0 (36.5-38.0)		**<0.001ᴍ**
SO_2 (%)	84.5 (50-94)	95.0 (80-97)		**<0.001ᴍ**
Respiratory rate (min)	29.5 (20-40)	16.0 (14-30)		**<0.001ᴍ**

CAD: Coronary artery disease, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease, CVE: Cerebrovascular event, DBP: Diastolic blood pressure, DM: Diabetes mellitus, HR: Heart rate, HT: Hypertension, SBP: Systolic blood pressure (Statistical analysis: t: t-test; χ^2: chi-square (Fisher's Exact test) ᴍ: Mann-Whitney U), t: t-test, SD: Standard deviation

Table 2. Hematological parameters of the patients according to their clinical status

Parameters	Critical Median (min-max)	Stable Median (min-max)	p
Endocan (ng/mL)	343.4 (187-2651)	223.3 (100-1923)	**<0.001**
CRP (mg/L)	84.0 (6-300)	27.0 (2.5-196)	**0.001**
Ferritin (µg/L)	470.0 (45-6396)	143.5 (17-2478)	**0.001**
PCT (µg/L)	0.11 (0.01-10)	0.01 (0.01-7.5)	**0.001**
Lactate (µg/L)	2.6 (1.2-21)	1.4 (0.8-3.4)	**0.001**
PaO_2/FiO_2	189.0 (98-306)	326.0 (131-457)	**0.001**
NLR	7.04 (1.8-53.3)	3.4 (1-12)	**0.001**
D-dimer (µg/L)	930.0 (200-11650)	391.0 (120-6918)	**0.001**
High-sensitivity troponin T (ng/L)	0.04 (0.04-0.35)	0.009 (0.01-0.064)	**0.001**
Urea (mg/dL)	52.5 (10-120)	32.5 (13-108)	**0.001**
Creatinine (mg/dL)	1.15 (0.65-1.8)	0.92 (0.5-2.0)	**0.005**
WBC (x10^9/L)	11.8 (4.3-22)	6.9 (3.4-18)	**0.001**
INR	1.11 (0.9-2.1)	0.99 (0.87-1.39)	**0.001**
AST (U/L)	38.0 (15-131)	26.5 (14-177)	**0.001**
ALT (U/L)	23.5 (8-133)	18.5 (7-120)	0.057

ALT: Alanine transaminase, AST: Aspartate aminotransferase, CRP: C-reactive protein, INR: International normalized ratio, NLR: Neutrophil-to-lymphocyte ratio, PCT: Procalcitonin, WBC: White blood cell. Statistical analysis: Mann-Whitney U test

Table 3. Thorax CT findings and treatment approach in patient groups

	Critical [n (%)]	Stable [n (%)]	Total [n (%)]	p
Thorax CT findings				
Mild	-	16 (36.4%)	16 (20.0%)	**0.001**
Moderate	13 (36.1%)	17 (38.6%)	30 (37.5%)	
Severe	23 (63.9%)	11 (25.0%)	34 (42.5%)	
Treatment approach				
Mechanical ventilation	18 (50.0%)	-	18 (22.5%)	**0.001**
Antiviral	36 (100%)	44 (100%)	80 (100%)	-
Antibiotics	27 (75.0%)	8 (18.2%)	35 (43.8%)	**0.001**
Steroid	34 (94.4%)	8 (18.2%)	42 (52.5%)	**0.001**
Anticoagulant	33 (91.7%)	13 (29.5%)	46 (57.5%)	**0.001**
High-flow oxygen therapy	30 (83.3%)	9 (20.5%)	39 (48.8%)	**0.001**
Positive inotropic agents	17 (47.2%)	1 (2.3%)	18 (22.5%)	**0.001**
Mortality	14 (38.9%)	-	14 (17.5%)	**0.001**

CT: Computed tomography; χ^2: chi-square (Fisher's Exact) test

that endocan, age, lactate and high-sensitivity troponin T showed significant effectiveness in distinguishing the groups in the multivariate model (p<0.05; Table 4).

It was determined that serum endocan levels higher than 244.9 ng/mL was significant in distinguishing the critically ill group from the stable patient group (p<0.05) (area under the curve: 0.75, confidence interval: 0.639-0.855) with sensitivity and specificity as 88.9% and 63.6%, respectively (Figure 1).

We analyzed whether there was a correlation between age and endocan level, but found no statistical correlation (p=0.313 correlation coefficient: -0.114) (not shown in the tables).

Table 4. Multivariate logistic regression analysis results of the parameters

Variables	Odds ratio	95% confidence interval Lower-upper	p
Endocan	**1.003**	**0.994-0.999**	**0.015**
Age	1.099	0.828-0.989	**0.028**
CRP	1.017	0.965-1.002	0.74
PCT	0.537	0.108-3.106	0.533
Ferritin	0.046	0.998-1.002	0.994
Lactate	1.861	0.040-0.610	**0.038**
NLR	0.184	0.646-1.070	0.152
D-dimer	0.999	0.999-1.003	0.160
High-sensitivity troponin T	70.12	0.100-0.440	**0.022**
INR	1.971	0.001-16.006	0.416

CRP: C-reactive protein, INR: International normalized ratio, NLR: Neutrophil-to-lymphocyte ratio, PCT: Procalcitonin. Nagelkerke R square =0.81

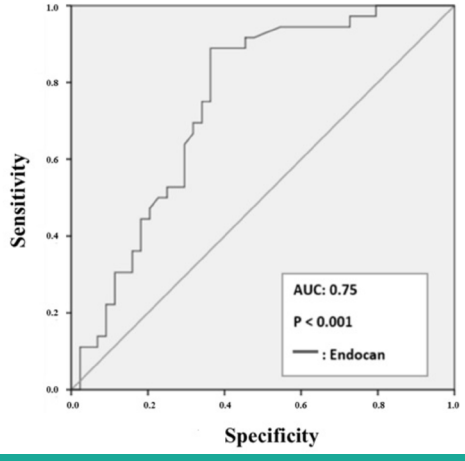

Figure 1. ROC curve analysis of endocan
ROC: Receiver operating characteristic

Discussion

In the present study, we aimed to investigate whether serum endocan levels may have a prognostic value in COVID-19 patients according to their clinical condition with regards to mortality and morbidity and endocan levels can be used to discriminate the clinical condition of the patients. Endocan levels of patients in critical condition were significantly higher than the patients with stable condition (p=0.000). Moreover, serum endocan levels higher than 244.9 ng/mL significantly distinguish the critically ill patient from the stable patient (p<0.001).

Various conditions related with endothelial dysfunction have been associated with elevated serum endocan levels (23-27). On the other hand, highly elevated endocan levels have been shown in other various conditions such as cancer (28,29), diabetes (30) and multiple sclerosis (31). Elevated levels of endocan in these conditions can be explained by both either the vascular inflammation due to the condition or the elevated expression levels of endocan by in the tissue itself (28-31).

COVID-19 has been associated with both macro/micro inflammation in both pulmonary and extrapulmonary vasculature (32) leading to thromboembolic complications that may be useful for prediction of prognosis of the patients (33). An earlier study reported a significant association between endocan levels and poor prognosis (7). Previously, it was shown that serum endocan levels are elevated in COVID-19 patients (34). Moreover, the first study reported that serum endocan levels of 276.4 ng/mL predicts poor prognosis with 97% sensitivity and 85% specificity (7) and the latter indicated serum endocan levels of 202 ng/mL at the admission predicts COVID-19 with 86.7% sensitivity and 50% specificity (34). In our study, we have found that serum endocan levels were significantly higher in the patients in critical condition and serum endocan levels of 244.9 ng/mL predicts the clinical status of the patients with 88.9% sensitivity and 63.6% specificity.

Several factors were investigated to predict the severity and outcomes of COVID-19 (35-39). In our study, multivariate logistic regression analysis revealed that endocan, age, lactate and high-sensitivity troponin T are associated with the clinical status of COVID-19 patients and that is in line with the previous studies (35-39).

In Liang et al.'s (40) study, which was defined as a composite measure of critical illness, ICU admission, invasive ventilation, or death among hospital-admitted COVID-19 patients, they found that increasing age and high

lactate level were associated with poor prognosis. Due to the decreasing vital capacity with advanced age, the clinical course is more severe in COVID-19 patients. In our study, we found that being old is associated with a poor prognosis. In addition, increased lactate levels associated with tissue perfusion impairment indicate a poor prognosis. These parameters were higher in the critically ill group compared to the stable group.

Study Limitations

Our study had several limitations. First of all, serum endocan levels were measured only on admission. Although the study primarily aimed to predictive capacity of the condition of a COVID-19 patient on admission, it could be relevant to take several measurements to make a comment on the correlation between the alterations in the endocan levels throughout the disease progression. Secondly, number of patients included in this study were low, therefore, statistical power for the analysis to check the relationship between factors, such as comorbid factors, and clinical status of the patients was low.

Conclusion

Our results suggests that serum endocan levels are useful to predict the patients' clinical condition on the admission and may predict the prognosis and outcomes of COVID-19 patients.

Ethics

Ethics Committee Approval: This prospective single-centered study was conducted between 01/01/2021 and 31/12/2021 after the approval by Clinical Research Ethics Committee of University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital (date: 22.12.2020, number: 1753).

Informed Consent: Required consent has been obtained.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.Ö., Concept: D.Ö., E.A., A.M., M.Ç., B.D., A.C., Design: D.Ö., E.A., A.M., M.Ç., B.D., A.C., Data Collection or Processing: D.Ö., E.A., A.M., M.Ç., B.D., A.C., Analysis or Interpretation: D.Ö., E.A., A.M., M.Ç., B.D., A.C., Literature Search: D.Ö., E.A., A.M., M.Ç., B.D., A.C., Writing: D.Ö., E.A., A.M., M.Ç., B.D., A.C.

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