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Original Article

Serum Endocan Levels on Admission Are Associated With Worse Clinical Outcomes in COVID-19 Patients: A Pilot Study

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Abstract

Thrombotic and embolic complications in the cardiovascular system are evident and associated with worse prognosis in coronavirus disease 2019 (COVID-19) patients. Endothelial-specific molecule 1 (endocan) plays a role in vascular pathology. We hypothesized serum endocan levels on admission are associated with primary composite end point (mortality and intensive care unit hospitalization) in COVID-19 patients. Patients (n = 80) with laboratory, clinical, and radiological confirmed COVID-19 were included in this cross-sectional study. Ten milliliter of peripheral venous blood were drawn within 24 hours of admission to estimate serum endocan levels. Data were analyzed using SPSS version 26.0 (IBM). Patients with the primary composite end point had significantly higher serum endocan levels than patients without (852.2 ± 522.7 vs 550.2 ± 440.8 ng/L, respectively; $P < .01$). In the logistic regression analysis, only increased serum endocan levels and increase in age were independent predictors of the primary composite end point ($P < .05$). In the receiver operating characteristics curve analysis, we found that a serum endocan level of 276.4 ng/L had a 97% sensitivity and 85% specificity for prediction of the primary composite end point. Baseline serum endocan levels may prove useful as a prognostic factor in patients hospitalized for COVID-19.

Keywords

endocan, COVID-19, SARS-CoV-2, mortality, intensive care, clinical outcome

Introduction

After severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) in the last 2 decades, the world is facing a new challenge with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or coronavirus disease 2019 (COVID-19) pandemic. The full range of COVID-19 manifestations is yet to be clarified. The classical symptoms are dry cough, high fever, dyspnea, and potentially lethal pneumonia, whereas many patients also have additional signs and clinical manifestations of isolated vasculopathy.[1] Cardiovascular (CV) thrombotic and embolic complications were evident in hospitalized COVID-19 patients.[2]

Serum endothelial-specific molecule-1 (endocan) levels have been found to be high in previous studies in many endothelium-related events such as endothelial dysfunction, hypertensive end organ damage, pulmonary embolism, acute coronary syndrome, and diabetic vasculopathy.[3-6] In our study, we hypothesized that serum endocan levels on admission are associated with the primary composite end point (mortality and intensive care unit hospitalization) in COVID-19 patients.

Methods

Study Population

Eighty patients admitted to the Emergency Department in Internal Medicine with laboratory and clinical and radiological of Istanbul University Faculty of Medicine confirmed COVID-19 were included in this retrospective cross-sectional study, which was conducted from March 11, 2020, to July 10, 2020.

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Patients were hospitalized if they have:

1. moderate/severe pneumonia (bilateral infiltration and/or multiple mottling and ground-glass opacity),
2. hypotension (<90/60 mm Hg) or tachypnea or hypoxemia (arterial oxygen (O_2) saturation below 93% without O_2 supply), or
3. mild pneumonia (unilateral infiltration) but having severe biochemical or hematological parameters such as ferritin value >1000 ng/mL or high-sensitivity C-reactive protein (hsCRP) >40 mg/dL or lymphopenia.

Patients were admitted to the intensive care unit, when any of the following clinical and laboratory parameters occurred:

- Respiratory rate $\geq$30/min
- Dyspnea
- SpO_2 <90% and PaO_2 <70 mm Hg despite >5 L/min nasal oxygen supply
- $PaO_2/FiO_2 \leq 300$
- Lactate >2 mmol/L
- Hypotension (systolic blood pressure <90 mm Hg or drop >40 mm Hg in usual systolic blood pressure or mean arterial pressure <65 mm Hg) and tachycardia (>100 beat/min)
- Findings showing renal, hepatic, hematological (thrombocytopenia), or cerebral (confusion) dysfunction (sepsis or septic shock)
- Skin findings of capillary return disorder such as cutis marmorata which is a skin finding of circulatory disorder and coldness.

Exclusion Criteria:

1. Severe chronic kidney disease (CKD) with measured or calculated glomerular filtration rate using the Cockcroft-Gault or Modification of Diet in Renal Disease (MDRD4) formula of <30 mL/min·1/73m2 or renal dialysis
2. Inflammatory diseases and/or malignancies in activity
3. Prior history of myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft operation, intermittent claudication, and transient ischemic attack or cerebrovascular accident
4. Diabetes mellitus with or without known organ damage

The enrolled patients were divided into 2 categories: 48 discharged without any complications and 32 who reached the primary end point (ie, mortality and intensive care unit hospitalization).

Data Collection

The demographic (age and sex), clinical (symptoms and outcomes) characteristics, and laboratory findings of patients during hospitalization were collected from medical records by 2 investigators (N.S. and A.A.). Radiological assessment included radiography, computed tomography, or magnetic resonance imaging. All data were independently reviewed and entered into a computer database by 2 analysts.

To confirm COVID-19, SARS-CoV-2 (2019-nCoV) qPCR Detection Kit (Bio-Speedy Bioeksen) was used for detecting the epidemic virus "SARS-CoV-2 (2019-nCoV)" causing COVID-19. The kit was applied to nucleic acid isolates from nasopharyngeal aspirate/lavage, bronchoalveolar lavage, nasopharyngeal swab, oropharyngeal swab, and sputum samples. Rapid diagnosis with the kit was achieved via 1-step reverse transcription (RT) and real-time qPCR (RT-qPCR) targeting SARS-CoV-2 (2019-nCoV)-specific RdRp (RNA-dependent RNA polymerase) gene fragment.

Serum Endocan Measurement

In order to estimate the serum levels of endocan, 10 mL of peripheral venous blood were drawn within 24 hours of admission, into plain blood collection tubes without any additives, and immediately immersed in melting ice and allowed to clot for 1 hour before centrifugation (1700 g at 4 °C for 10 minutes). Serum was then stored at −80 °C until analyzed, and samples were thawed only once. Endocan levels were measured using an enzyme-linked immunosorbent assay (Endocan ELISA kit, Bioassay Technology Laboratory). Measurements of cardiac enzymes and other biochemical parameters were performed using standard laboratory techniques.

Statistical analysis. Descriptive statistics were obtained for all study variables. All categorical variables were compared for the study outcome by using the Fisher exact test or χ^2 test, and continuous variables were compared using the t test or the Mann-Whitney U test, as appropriate. Continuous data are expressed as mean (SD) values. Variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov–Simonov/Shapiro–Wilk test) to determine whether they were normally distributed.

Categorical data are expressed as proportions. The Pearson correlation coefficient and Spearman rank correlation coefficient were used for liner correlation analysis. Independent sample t test was used to compare means of serum endocan levels in groups. Receiver operating characteristics (ROC) curve analysis was used to determine the optimal cutoff value of endocan for prediction of primary composite end point, and possible confounding factors were tested in logistic regression analysis for independent predictors of primary composite end point. Data were analyzed using SPSS version 26.0 (IBM). For all the statistical analyses, a 2-sided $P < .05$ was considered significant.

Results

Characteristics of the Patients With and Without the Primary Composite End Point

Eighty patients admitted to the COVID-19 service between March 11 and July 10 who met the inclusion and exclusion

Table 1. Baseline Characteristics, Signs, and Symptoms of the Patients.

	Patients, n (%)			
All (n = 80)		Primary composite end point		*P*
Characteristics		With (n = 32)	Without (n = 48)	
Age, Mean ± SD, years	62 ± 16	67 ± 14.2	59.6 ± 17.5	**.03**
Male	52 (65%)	25 (78%)	27 (56%)	.06
Smoking	9 (11%)	3 (9%)	6 (12%)	.73
Signs and symptoms at admission				
Fever	54 (67.5%)	22 (68%)	32 (66%)	.84
Cough	58 (72.5%)	25 (78%)	33 (68%)	.44
Sputum production	1 (1.3%)	0	1 (1.3%)	.98
Shortness of breath	49 (61.3%)	23 (71%)	26 (54%)	.16
Fatigue	64 (80%)	28 (87%)	36 (75%)	.25
Nausea	15 (18.8%)	4 (12%)	11 (22%)	.38
Diarrhea	10 (12.5%)	3 (9%)	7 (14%)	.73
Anosmia	4 (4%)	1 (1.3%)	3 (6%)	.64
Saturation, mean ± SD (%)	92 ± 6	89 ± 7.2	93.7 ± 4	.001
SBP, mean ± SD (mm Hg)	136 ± 26	133 ± 30	139 ± 23	.32
DBP, mean ± SD (mm Hg)	79 ± 13	76 ± 13	80 ± 13	.15
Pulse, mean ± SD (bpm)	95.5 ± 16.5	96.5 ± 16.1	94.5 ± 16.7	.60
RR, Mean ± SD (/min)	22.3 ± 5.4	24.6 ± 5.7	20.9 ± 4.6	.01

Abbreviations: DBP, diastolic blood pressure; RR, respiratory rate, SBP, systolic blood pressure.

Table 2. Important Laboratory Findings of the Patients With and Without Primary Composite End Point.

Parameters	Patients with primary composite end point	Patients without primary composite end point	*P*
Neutrophil/μL	6624 ± 4278	5427 ± 3523	.17
Glucose, mg/dL	137 ± 51	141 ± 59	.75
ALT, U/L	33 ± 25	41 ± 21	.59
AST, U/L	41 ± 26	36 ± 32	.47
ALP, U/L	76 ± 46	87 ± 48	.32
GGT, U/L	50 ± 44	60 ± 32	.56
C-reactive protein, mg/L	102 ± 96	65 ± 58	.07
Ferritin, ng/mL	665.7 ± 586.7	410 ± 380.3	.05
Procalcitonin, ng/mL	0.7 ± 0.4	0.4 ± 0.3	.22
D-dimer, μg/L	2446 ± 2450	1422 ± 1368	.14
hsTNT, pg/mL	53.6 ± 37.4	48.04 ± 17.2	.64
NT Pro-BNP, pg/mL	1755 ± 3644	1621 ± 3805	.87
Fibrinogen, mg/dL	531 ± 177.5	513 ± 173.2	.64
Endocan, ng/L	852.2 ± 522.7	550.2 ± 440.8	**<.01**

Abbreviations: ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; Endocan, endothelial specific molecule-l; GGT, gamma-glutamyl transferase; hsTNT, high-sensitivity troponin T; NT pro-BNP, N terminal pro B type natriuretic peptide.

criteria were included in the study. Baseline characteristics, signs, and symptoms of the patients are shown in Table 1. The mean age of the study population was 62 ± 16 years. There was a significant difference between the mean age of patients with and without the primary composite end point (67 ± 14.2 vs 59.6 ± 17.5 years, $P = .03$, Table 1). The study population was male-dominant (65%), but this was not significant ($P > .05$) (Table 1). There was no significant difference between the proportions of smokers in patients with the primary composite end point and those without ($P > .05$; Table1). Saturation was significantly lower and respiratory rate was significantly higher in patients with the primary composite end point compared with those without (89 ± 7.2 vs 93.7 ± 4%, $P = .001$, and 24.6 ± 5.7 vs 20.9 ± 4.6 per minute, $P < .01$, respectively; Table 1).

Laboratory findings are shown in Table 2. Serum neutrophil, glucose, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, C-reactive protein (CRP), ferritin, D-dimer, high-sensitivity troponin T (hsTNT), N-terminal pro-B type natriuretic peptide (NT Pro-BNP), fibrinogen, procalcitonin, and endocan levels were compared in patients with and without the primary composite end point (Table 2). Only serum endocan levels were significantly different between the 2 groups (852.2 ± 522.7 vs 550.2 ± 440.8 ng/L in patients with vs without the end point, respectively; $P < .01$; Table 2).

Table 3. Treatments of the COVID-19 Patients With and Without Primary Composite End Point.

	Patients, n (%)			
	Primary composite end point			
Characteristic	All (n = 80)	With (n = 32)	Without (n = 48)	*P*
Treatment				
Hydroxychloroquine	79 (99.6%)	32 (100%)	47 (99.5%)	.63
Antibiotic treatment	78 (97.5%)	31 (97%)	47 (98%)	.58
Antiviral treatment	41 (51%)	26 (83%)	15 (31%)	<.001
Anti-cytokine treatment	18 (22%)	14 (43%)	4 (8%)	.001
High-flow oxygen nasal cannula	27 (33%)	24 (60%)	3 (6%)	<.001
Invasive mechanical ventilation	27 (33%)	27 (84%)	0 (0)	<.001
Extracorporeal membrane oxygenation	4 (5%)	4 (12%)	0 (0)	<.001

Abbreviation: COVID-19, coronavirus disease 2019.

Table 4. Clinical Outcomes of the Patients.

Clinical outcomes	All (n = 80)	Patients with primary composite end point (n = 32)	Patients without primary composite end point (n = 48)	*P*
Hospital stay duration (days), mean ± SD	19.1 ± 13.4	27.9 ± 15.6	13.3 ± 7.3	.001
Mortality, n (%)	13 (16%)	13 (40%)	0	
Intensive care unit admission, n (%)	32 (40%)	32 (100%)	0	

Table 5. Correlations Between Endocan, Inflammatory Markers, NT-proBNP, and hsTNT.

		hsTNT	NT Pro-BNP	D-dimer	Ferritin	Procalcitonin	CRP
Endocan	Correlation Coefficient (r)	−0.10	−0.07	0.09	0.18	0.34	0.22
	P	.36	.50	.39	.10	.41	.03

Abbreviations: CRP, C-reactive protein; Endocan, endothelial specific molecule-1; hsTNT, high-sensitivity troponin T; NT pro-BNP, N-terminal pro-B type natriuretic peptide.

Treatments

Treatments of the COVID-19 patients with and without primary composite end point are shown in Table 3. Antiviral, anti-cytokine, high-flow oxygen cannula, invasive mechanical ventilation, and extracorporeal membrane oxygenation treatments were significantly more frequent in patients with the primary composite end point.

Clinical Outcomes

Hospital stay was significantly longer in patients with the primary composite end point compared with those without (27.9 ± 15.6 vs 13.3 ± 7.3 days, respectively, $P < .001$; Table 4). Thirteen of the 80 patients included in the study died and 32 needed to be admitted to the intensive care unit (Table 4).

Correlations Between Serum Endocan Level, Inflammatory Parameters, hsTNT, and NT-ProBNP

Correlations between serum endocan levels, inflammatory markers, NT pro-BNP, and hsTNT are shown in Table 5. There was only a weak-positive correlation between serum endocan levels and CRP ($r = 0.22$, $P = .03$; Table 5).

Independent Predictors for the Primary Composite End Point

In the logistic regression analysis, increased serum endocan levels and older age were independently related to the primary composite end point after controlling for the effects of the serum CRP, procalcitonin, ferritin, hsTNT, NT pro-BNP, and arterial saturation on admission (Table 6).

Receiver operating characteristics curve analysis showed that 276.4 ng/L of serum endocan level had a 97% sensitivity and 85% specificity for prediction of the primary composite end point (Figure 1).

Discussion

In our study, the relationship between serum endocan levels and poor clinical course in COVID-19 disease, which has never been investigated before, was studied. There was a significant

Table 6. Logistic Regression Analysis to Predict Independent Variables for the Primary Composite End Point.

			95% CI	
Variables	*P*	Odds Ratio	Lower	Upper
Endocan	**.01**	1.002	1.000	1.003
CRP	.81	1.001	0.994	1.008
Procalcitonin	.79	0.928	0.535	1.611
Ferritin	.10	1.001	1.000	1.002
hsTNT	.32	0.997	0.991	1.003
NT pro-BNP	.77	1.000	1.000	1.000
Age	**.02**	1.054	1.007	1.103
SaO_2	.05	0.891	0.793	1.001

Abbreviations: CRP, C-reactive protein; Endocan, endothelial specific molecule-1; hsTNT, high-sensitivity troponin T; NT pro-BNP, N terminal pro B type natriuretic peptide; SaO2< arterial saturation on admission.

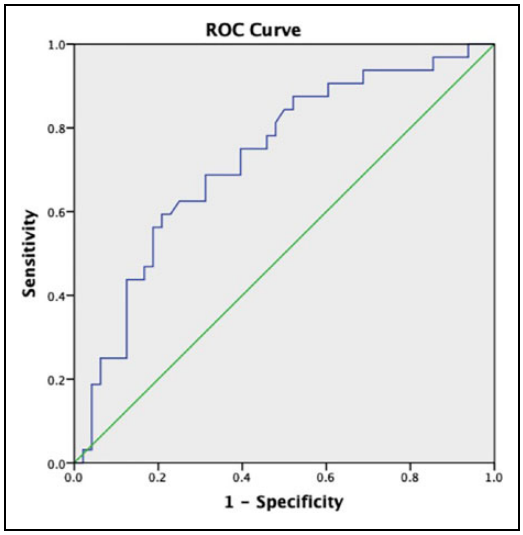


Figure 1. The receiver operating characteristics (ROC) curve analysis of Endocan for prediction of primary composite end point.

relationship between serum endocan levels and the primary composite end point consisting of the need for intensive care unit and mortality.

The COVID-19 disease has many different clinical manifestations. The course of the disease, ranging from small vessel embolism to large vessel thrombosis, can vary in clinical spectrum, suggesting that vascular inflammation may occur in the development of the disease. In addition, the presence of very high D-dimer levels during the course of the disease is another event that suggests vascular inflammation has an important role in the pathogenesis of the disease.[7]

The endothelium has a glycocalyx stratum and secretes tPA (tissue plasminogen activator) that inhibits binding of platelets or induction of the coagulation cascade.[8-13] In the previous SARS outbreak, SARS-CoV virion was demonstrable in endothelial cells.[14] The angiotensin-converting enzyme 2 (ACE 2) receptor for SARS-CoV-2 exists in endothelial cells.[15] Previous studies have demonstrated SARS-CoV-2 like virion in endothelial cells.[16,17] Angiogenesis in COVID-19 has also been linked to endothelial invasion by SARS-CoV-2, with subsequent severe endothelial damage and associated disruption of cellular membranes.[18] The endothelial dysfunction leads to the loss of the antithrombotic function of these cells, predisposing to thrombus formation.[19] Endothelial disruption leads to massive release on von-Willebrand factor.[20] Abnormal vessel wall, hyperviscosity, immune activation, increased fibrinogen levels, hypoxia, turbulent flow, hypercoagulation due to platelet activation, complement activation, and hyperimmune response have been reported in relation to COVID-19.[20]

All these endothelial factors can initiate thrombosis. The propagation of thrombosis can be facilitated by the inflammation induced by endothelial dysfunction. Endothelial cells release interleukin-6 in response to the virus invasion that augments the host immune response, even to the cytokine storm syndrome.[21] Though immune complex vasculitis has been claimed as a pathological mechanism for COVID-19, the evidence is limited at present.[22] Severe COVID-19 leads to a cytokine storm and coagulopathy is a known consequence of acute sepsis.[23] This underlying coagulation cascade activation predisposes to disseminated intravascular coagulation.[24]

Endocan plays an important role in vascular pathologies. It has been demonstrated in many pathologies such as atherosclerosis, diabetic vasculopathy, vascular invasion in malignancies and new vascular formation, vascular thrombosis, acute coronary syndrome, and pulmonary embolism.[3-6]

Serum endocan levels are increased in diseases with vascular involvement or invasion.[25,26] A study showed that there was a significant correlation between endocan messenger RNA (mRNA) levels and intratumoral microvessel density, mRNA of vascular endothelial growth factor, and vascular or venous invasion.[25] A previous study also demonstrated that serum endocan levels increased in the presence of low glomerular filtration rate and were positively associated with markers of inflammation, all-cause mortality and CV outcomes in patients with CKD, independently of conventional, and nonconventional risk factors.[27] In the light of this study, one of the exclusion criteria of our study was CKD, as it is an independent cause of high plasma endocan levels.[27]

Our study has some strengths. First, we only enrolled hospitalized patients who had laboratory-confirmed COVID-19 pneumonia. Second, every patient underwent serum endocan level measurement from the first admission. On the other hand, the present study also has several limitations. First, because of the retrospective nature of this study, patients were selected by the investigators and this can cause bias. Second, the information on follow-up serum endocan levels during the clinical course of the disease to track dynamic changes would have increased the power of the study.

In conclusion, we found a significant relationship between serum endocan levels and the primary composite end point consisting of the need for intensive care unit and mortality.

In the logistic regression analysis, only increased serum endocan levels and increase in age were independent predictors for the primary composite end point ($P < .05$). In the ROC analysis, a serum endocan level of 276.4 ng/L had a 97% sensitivity and 85% specificity for prediction of the primary composite end point. Therefore, serum levels of endocan, a new biomarker of endothelial pathology, may be useful as a prognostic factor in patients hospitalized for COVID-19. Additional studies should be conducted to assess any predictive role of endocan levels.

Authors' Note

All authors contributed to (1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, and (3) final approval of the version to be published.

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