ORIGINAL ARTICLE

Evaluation of endostatin levels in COVID-19 patients admitted to the emergency department

Évaluation des niveaux d'endostatine chez les patients atteints de COVID-19 admis aux urgences

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Abstract

Introduction: The COVID-19 is defined as a respiratory and endothelial disease caused by Severe Acute Respiratory Syndrome Coronavirus 2. Endostatin is a molecule bound to collagen in the basal membrane of endothelial cells.
Objective: The aim of this study was to measure the serum endostatin levels of patients diagnosed with COVID-19 in the emergency department.
Methods: This study was conducted in the emergency department with two groups: COVID-19 PCR-positive patients and healthy adults. Complete blood count, serum biochemistry values, and radiological imaging results were evaluated. Serum endostatin levels were measured from venous blood samples collected during the emergency department visits. Data were analyzed using the SPSS 19.0 software.
Results: A total of 148 COVID-19 patients and 35 healthy controls were included in the study. The serum endostatin levels of the COVID-19 patient group were significantly lower compared to the healthy control group ($p<0.05$). The Chest CT Severity Score, 4C-Mortality Score, Quick SOFA, and Quick COVID-19 Severity Index were significantly higher in the patients with a fatal outcome compared to those who survived ($p<0.001$). Although serum endostatin levels were slightly higher in the fatal outcome group, no statistically significant difference was observed ($p>0.05$).
Conclusion: There is no increase in serum endostatin levels in patients with COVID-19 presenting to the emergency department. While a slight increase in endostatin levels was observed in patients with a fatal outcome, it is believed that endostatin will not be effective in predicting prognosis.

Keywords: COVID-19, Emergency Department, Endostatin, Pulmonary Injury, Prognosis

Résumé

Introduction : La COVID-19 est une maladie respiratoire et endothéliale causée par le SARS-CoV-2. L'endostatine, une molécule liée au collagène dans la membrane basale des cellules endothéliales, joue un rôle dans l'angiogenèse et l'inflammation.
Objectif : L'objectif de cette étude était de mesurer les niveaux sériques d'endostatine chez les patients diagnostiqués avec la COVID-19 dans le service des urgences.
Méthodes : Cette étude a inclus deux groupes : des patients PCR-positifs pour la COVID-19 et des adultes sains. Les données cliniques, la numération formule sanguine, les valeurs biochimiques sériques et les résultats radiologiques ont été recueillis. Les niveaux sériques d'endostatine ont été mesurés à partir de sang veineux lors des consultations aux urgences.
Résultats : Un total de 148 patients atteints de la COVID-19 et 35 témoins sains ont été inclus. Les niveaux d'endostatine sériques étaient significativement plus faibles chez les patients COVID-19 comparés au groupe témoin ($p<0,05$). Le score de gravité au scanner thoracique, le score 4C de mortalité, le Quick SOFA et l'indice de gravité rapide COVID-19 étaient plus élevés chez les patients décédés que chez ceux ayant survécu ($p<0,001$). Bien que les niveaux d'endostatine aient été légèrement plus élevés dans le groupe fatal, aucune différence statistiquement significative n'a été observée ($p>0,05$).
Conclusion : Il n'y a pas d'augmentation des niveaux d'endostatine chez les patients atteints de la COVID-19 aux urgences. L'endostatine semble inefficace pour prédire le pronostic.

Mots clés: COVID-19, Service des urgences, Endostatine, Lésion pulmonaire, Pronostic

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What is known

Very few studies report that serum endostatin levels are high in COVID-19 patients followed up in intensive care and in patients presenting with acute dyspnea in the emergency department.

What this article adds

Serum endostatin levels in COVID-19 patients presenting to the emergency department are not higher than in healthy individuals.

Introduction

The Coronavirus Disease (COVID-19), which spread worldwide in a short time, is defined as a respiratory and endothelial disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), characterized by coagulopathy and an inflammatory syndrome (1,2). Its clinical forms can range from asymptomatic-mild upper respiratory tract infection to severe viral pneumonia resulting in sepsis, multiple organ failure, and even death. Severe and critical disease occurs in approximately 20% of cases (3,4). COVID-19 can lead to serious clinical conditions such as Acute Respiratory Distress Syndrome (ARDS), acute kidney injury, arrhythmia, acute cardiac injury, cardiomyopathy, and pulmonary embolism (4,5). The virus enters the cells through functional Angiotensin Converting Enzyme 2 (ACE2) receptors in the respiratory tract, replicates, and attracts monocytes, macrophages, and T cells, which lead to a severe inflammatory process. This triggers excessive cytokine release. It is suggested that this process leads to endothelial cell damage (6). Endothelial damage, microvascular inflammation, endothelial exocytosis, and/or endotheliali tis are thought to play a central role in the pathogenesis of ARDS and organ failure in severe COVID-19 cases. Although it is stated that COVID-19 represents an endothelial disease, the exact pathogenesis and its harmful outcomes in COVID-19 remain uncertain (2,7,8,9,10,11).

Endostatin is a molecule bound to collagen in the basal membrane of endothelial cells. It acts as an anti-angiogenic protein by inhibiting endothelial cell proliferation and migration (12,13). It has been reported in the literature that endostatin levels can predict adverse outcomes related to long-term hypertension, hypertensive target organ damage, decreased glomerular filtration rate, myocardial infarction, and stroke (14).

There are very few studies in the literature evaluating endostatin levels in COVID-19 patients. No studies have been conducted on emergency department patients. In this study, endostatin levels, which are said to indicate vascular endothelial damage, were evaluated in patients with COVID-19 infection in the emergency department. Considering that emergency departments were overwhelmed with patient admissions far beyond their capacity during the COVID-19 pandemic, a marker that could predict the prognosis of the disease is believed to be of significant contribution to the management of the disease. The aim of our study was to determine serum endostatin levels in COVID-19 patients and investigate whether it could contribute to predicting the disease's.

Methods

This study was conducted as a prospective case-control study with the permission of the Clinical Research Ethics Committee of Canakkale Onsekiz Mart University (Decision No: 2020-04) at the emergency department of Canakkale Onsekiz Mart University Hospital and the laboratory of the Experimental Research Application and Research Center of Canakkale Onsekiz Mart University.

A total of 150 patients aged 18 and over, who tested positive for COVID-19 PCR between 01.04.2021 and 01.07.2021, were included in the study. In contrast, a control group was formed with 35 healthy individuals over the age of 18, who had no known diseases and no history of medication use, and who were not suspected of having COVID-19.

Patients under the age of 18, those with a negative PCR test, patients in arrest or intubated status at the time of presentation, those who wished to withdraw from the study, and those with incomplete medical examination records or test results in the hospital records, were excluded from the study. Patients diagnosed with acute cerebrovascular disease, acute coronary syndrome, acute renal failure, acute pulmonary embolism, ARDS, sepsis, and known malignancies were also excluded. The aim was to predict the prognosis of patients without complications, and patients with complications were not included in the study.

In accordance with clinical routine, emergency department triage personnel measured vital parameters such as heart rate, respiratory rate, systolic blood pressure, and diastolic blood pressure. Blood pressure was measured in a supine position using an oscillometric non-invasive technique after a 5-minute rest. Respiratory rate was measured by visual inspection of chest movements for one minute while the patients were lying still and avoiding talking. Pulse oxygen saturation was measured as a percentage (SpO2) after the patient had been in a supine position for 5 minutes. Heart rate and SpO2 measurements were taken with a patient bedside/ portable monitor (IntelliVue MP70-Philips Medical Systems, Boblingen, Germany) attached to the second or third finger of the left hand. Values were recorded once a stable reading was obtained on the monitor or after a 15-second wait.

The epidemiological characteristics of the patients (age, gender, occupation, habits, etc.), vital signs (blood pressure, pulse, respiratory rate, body temperature, SpO2 level), anamnesis, and physical examination findings were recorded in pre-prepared forms. Routine care, evaluation, and treatment in the Emergency Department were carried out independently of the study. Patients' routine biochemical and hemogram parameters, radiological imaging results, and other data were recorded from the hospital's electronic data system.

Eight cc of venous blood samples were taken from the participants in both the patient and control groups, and after centrifuging at 4000 rpm for 4 minutes, the serum

sample was stored in an Eppendorf tube at -80°C for later measurement of serum endostatin levels. Serum endostatin levels were measured in the laboratory of the Experimental Research Application and Research Center of Canakkale Onsekiz Mart University without knowledge of the group assignments. Endostatin levels were measured using an ELISA kit (Elisa Kit/96 Test/ABCAM).

Scoring Systems Calculation

To evaluate pulmonary involvement in the disease, a semi-quantitative scoring system, the Chest CT Severity Score (CT-SS), was used. CT-SS is a commonly used scoring tool to assess the severity of lung involvement in high-resolution chest CT scans [15]. This severity score was calculated by evaluating the extent of lung involvement for each of the five lung lobes on a 0-5 scale: 0 = no involvement, 1 = less than 5%, 2 = 5-25%, 3 = 26-49%, 4 = 50-75%, and 5 = more than 75%. The sum of the scores for all five lobes gives the total CT-SS, which ranges from 0 (no involvement) to 25 (maximum involvement). Based on the CT-SS score range, patients were classified as having mild (0-10) or severe (11-25) disease.

To evaluate patients' clinical conditions, the 4C Mortality Score, qSOFA (Quick SOFA), and qCSI (Quick COVID-19 Severity Index) scores were calculated.

The qSOFA score is calculated by assigning 1 point for each of the following parameters: respiratory rate ≥22 breaths/min, Glasgow Coma Scale (GCS) <15, and systolic blood pressure (SBP) ≤100 mmHg [16].

In calculating the qCSI score, nasal cannula flow rate, respiratory rate, and the lowest measured SpO2 were used. For respiratory rate: ≤22 breaths/min = 0 points, 22-38 breaths/min = 1 point, >28 breaths/min = 2 points. For SpO2: >92% = 0 points, 89-92% = 2 points, ≤88% = 5 points. For O2 flow rate: ≤2 L/min = 0 points, 3-4 L/min = 4 points, 5-6 L/min = 5 points. The qCSI score was interpreted as follows: ≤2 = low risk, 3-5 = low-moderate risk, 6-8 = moderate-high risk, >9 = high risk [17].

The 4C Mortality Score consists of eight parameters: gender (male = 1, female = 0), number of comorbidities (no comorbidities = 0, 1 comorbidity = 1, ≥2 comorbidities = 2), respiratory rate (<20 breaths/min = 0, 20-29 breaths/min = 1, >30 breaths/min = 2), SpO2 in room air (≥92% = 0, <92% = 2), GCS (15 = 0, <15 = 2), urea (mmol/L) (<7 = 0, 7-14 = 1, >14 = 3), CRP (mg/dL) (<50 = 0, 50-99 = 1, ≥100 = 2). The total score was categorized as follows: 0-3 points = low risk, 4-8 points = moderate risk, 9-14 points = high risk, and ≥15 points = very high risk [18].

Statistical Analysis

Data were analyzed using the SPSS version 19.0 software. Descriptive data were presented as numbers, percentages, means, standard deviations, medians, minimums, and maximums. The Chi-square test was used for the comparison of categorical data, and the Student's t-test and Mann Whitney U test were used for the comparison of quantitative data. A p-value of <0.05 was considered statistically significant.

Results

A total of 183 participants were included in the study, consisting of 148 COVID-19 PCR-positive patients and 35 healthy controls. 54.3% of the COVID-19 patient group and 48% of the control group were female (p=0.810). The mean age of the patient group was 53.9±14.5 years, while the mean age of the control group was 51.5±22.4 years (p=0.426). Serum endostatin levels were found to be higher in the healthy control group compared to the COVID-19 patient group (50.7) (p=0.023) (Table 1).

Table 1. Comparison of age, gender, and endostatin levels between the COVID-19 patient group and the control group.

Parameters	COVID Positive (n=148)	Control-Healthy (n=35)	P
Age Mean±SS	53.9±14.5	51.5±22.4	0.426
GenderWomen/Man (%)	77/71(54.3/45.7)	19/16(52.0/48.0)	0.810
Endostatin ng/mL	50.7(41.2-62.4)	59.9(42.9-401.9)	0.023

SS:Standart deviation

p<0.05 Statistically significant

14 patients (9.5%) with COVID-19 infection experienced mortality. When evaluating the presence of chronic diseases, the rate of hypertension in the deceased patient group due to COVID-19 was 64.3%, while in the surviving patient group it was 36.6% (p=0.043). The clinical characteristics of the patients with fatal outcomes are presented in Table 2.

Table 2. Clinical characteristics of COVID-19 infected patients with survival and fatal outcomes.

Parameters		Living Patients n=134 (% 90.5)	Mortality Patients n=14 (% 9.5)	P
Age Mean±SS		53.62±13.98	59±16.9	0.166
Gender n (%)	E	62(46.3)	9(64.3)	0.199
	K	72(53.7)	5(35.7)	
Hypertension n (%)		49(36.6)	9(64.3)	0.043
Temperature Median (IQR)		36.6(36.4-36.8)	36.8(36.7-36.9)	0.049
Respiratory Rate/dk Median (IQR)		18(16-20)	25.5(22-26)	<0.001
Heart Rate/dk Median (IQR)		85(78-93)	96.5(85-112)	0.005
Saturation % Median (IQR)		97(93-98)	77.5(65-84)	<0.001

p<0.05 Statistically significant

Plasma leukocyte count (10^3/µL), CRP (mg/dL), ferritin (ng/mL), Troponin (ng/L), D-dimer (ng/mL), and urea (mg/dL) levels were higher in the patients with fatal outcomes (p<0.05). In contrast, lymphocyte (10^3/µL) and albumin (g/L) levels were lower in the patients with fatal outcomes. The median serum endostatin level in the surviving patients was 50.4 ng/mL (41.0-62.1), while in the fatal outcome group it was 54.4 ng/mL (46.9-79.5) (p=0.174). (Table 3).

Table 3. Laboratory parameters of COVID-19 infected patients with survival and fatal outcomes.

Laboratory parameters	Living Patients (IQR)	Mortality Patients (IQR)	p
WBC (10^3/uL) Median (IQR)	6.1(4.6-8.1)	8.4(5.9-12.5)	0.010
CRP (mg/dL) Median (IQR)	3.3(0.8-8.5)	13.9(10.8-22.8)	<0.001
Ferritin (IQR)	240.9 (105.7-541.2)	634(371-2000)	0.001
Tn(IQR) (ng/L) (IQR)	7.4(5-11.5)	23.3(9.6-100.8)	<0.001
D-Dimer (ng/mL) (IQR)	0.4(0.3-0.7)	0.8(0.7-2.9)	<0.001
Urea (IQR)	26.8(19.6-37.1)	36.3(24.1-78.2)	0.019
Lymphocyte (IQR)	1.37(1-1.9)	0.7(0.4-0.9)	<0.001
Albumin (g/L) Mean±standard deviation	3.97±0.5	3.4±0.5	<0.001
Endostatin (IQR)	50.4(4.1-62.1)	54.4(46.9-79.5)	0.174

WBC: White Blood Cell
CRP: C reactive Protein
Tn: Troponin
IQR:İnterquartile range, **WBC**: leukocyte , **CRP**: C reactive protein, Tn: troponin
p<0.05 Statistically significant

When the scoring systems applied to COVID-19 patients were compared between the deceased and surviving patient groups, it was observed that the scores of the deceased group were higher (p<0.001) (Table 4).Thirteen patients (8.8%) in the COVID-19 patient group were followed in the intensive care unit (ICU). The median serum endostatin level of patients who were not admitted to the ICU was 50.61 ng/mL (40.85-62.12), while the median level of those admitted to the ICU was 52.55 ng/mL (49.55-79.45) (p=0.175).

Table 4. Comparison of scoring systems in covid-19 infected patients with surviving and fatal outcomes

Score Systems	Living Patients (IQR)	Mortality Patients (IQR)	P
CT-SS	8,0 (4,0-12,0)	22,0 (18,0-23,0)	<0,001
4C-Mortality Score	4,0 (1,0-7,0)	11,0(9,0-14,0)	<0,001
Quick SOFA	0,0(0,0-0,0)	1,0(1,0-1,0)	<0,001
Quick COVID-19 Severity Index	0,0(0,0-0,0)	11,0(10,0-11,0)	<0,001

CT-SS: Chest CT Severity Score
p<0.05 Statistically significant

Lung involvement was observed in 121 (81.8%) patients. When the endostatin levels of the groups with and without lung involvement were compared, no significant difference was found (p=0.394) (Table 5).

Table 5. Comparison of COVID-19 infected patients with and without lung involvement.

Variable	Lung involvement positive (n=27)	Lung involvement negative (n=121)	p
Endostatin	50.12 (43.48-76.03)	50.67 (40.85-61.55)	0.379
Age	45.0 (37.0-59.0)	56.0 (45.5-63.0)	0.025
qSOFA	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.054
4Cmortality score	1.0 (0.0-5.0)	5.0 (2.0-9.0)	<0.001
Quick COVID-19 Severity Index	0.0 (0.0-0.0)	0.0 (0.0-2.0)	0.007
Mortality n (%)	1 (7.1)	13 (92.9)	0.258

p<0.05 Statistically significant

Discussion

In this study, we aimed to determine the serum endostatin levels of COVID-19 patients in the emergency department and investigate its effectiveness in predicting the prognosis. We believe our findings are valuable, as there are no studies directly assessing serum endostatin levels in COVID-19 positive patients in the emergency department.

As of January 16, 2025, according to the World Health Organization (WHO) data, a total of 777,126,421 confirmed cases and 7,079,925 deaths have been reported due to COVID-19 (19). COVID-19 patients have caused an increase in the workload of health systems worldwide and disruptions in the delivery of adequate healthcare services to patients.

In general, emergency departments are a significant source of hospital admissions. Early detection of emergency department patients who require hospitalization allows for more efficient use of hospital resources [20]. It is also known that increased patient volume in emergency departments is associated with worse patient outcomes [21]. Therefore, in a healthcare system where a large number of patients like COVID-19 are being admitted, there is a need for markers that can differentiate the severity of these patients.

There is evidence that the SARS-CoV-2 virus, the causative agent of COVID-19, directly invades endothelial cells, leading to cell damage. In severe COVID-19 cases, this damage is thought to play a role in the pathogenesis of acute respiratory distress syndrome and organ failure [2,7,8]. Although studies support the hypothesis that coagulopathy can be induced by endothelial damage and may exacerbate the severity of COVID-19, the exact pathogenesis of endothelial damage and its harmful effects in COVID-19 remain uncertain and are still being studied [9,10,11].

A study examining the relationship between plasma endostatin levels and 90-day mortality in patients presenting to the emergency department with acute dyspnea found that higher mortality was associated with elevated endostatin levels in the blood [22]. In this study, the average age of the patients was 74.5, with 56% requiring hospitalization and 25% being followed in a monitored observation unit [22]. In our study, the

average age, hospitalization rate, and the number of patients requiring intensive care were lower than in the study by Carlsson et al. The reason for this difference was that the patients presenting with dyspnea in our study had advanced age and a variety of etiologies.

In this study, it was suggested that angiogenesis and extracellular matrix disruption might contribute to the elevation of endostatin levels in the presence of severe dyspnea. This study, however, included patients with various causes of dyspnea (such as heart failure, pulmonary embolism, etc.), whereas our study was focused specifically on COVID-19 patients. Given that each cause of dyspnea has different pathophysiological characteristics, we believe that studying serum endostatin levels in each specific disease group would yield more accurate and reliable results. It is accepted that the origin of circulating endostatin in the blood is unclear and that it is not tissue-specific (14). In our study, as no significant elevation in serum endostatin levels was observed, we believe that it should be studied in more specific disease groups.

In a study by Shah et al., it was shown that endostatin levels in healthy individuals did not vary according to sex, anthropometric, or physical characteristics (23). It is noted that hypoxia, particularly in healthy individuals, increases endostatin expression and secretion [24, 25, 26].

In a study by Sana Asif et al., who assessed plasma endostatin levels in COVID-19 patients admitted to intensive care, they found that endostatin levels were associated with hypoxia and inflammation and could predict short-term mortality in intensive care. They suggested that this mediator could be a useful marker for the severity of disease in COVID-19 [25].

Our aim was to investigate whether plasma endostatin levels could be useful in predicting the need for hospitalization or mortality in COVID-19 patients presenting to the emergency department who did not yet require intensive care. All studies on endostatin levels in COVID-19 patients in the literature so far have been conducted on patients in intensive care. In our study, however, endostatin levels were assessed at the initial presentation to the emergency department, before intensive care was required. The main reason for the discrepancy between our results and the literature may be related to the course of the disease. Future studies should consider this aspect and plan research including serial measurements.

Although serum endostatin levels showed a slight increase in patients who died, compared to those who survived, it was not statistically significant. We believe that the initially slightly elevated values may rise as the disease progresses.

In summary, our findings differ from those of ICU-based studies, likely due to the earlier disease stage of our patients, who presented to the emergency department without acute complications [22,25]. While previous research focused on critically ill patients with extensive inflammation and hypoxia, our cohort mostly consisted of stable individuals with mild to moderate disease. Moreover, we did not perform serial measurements, which could have revealed rising endostatin levels over time. The relatively small control group and absence of multivariate analysis also limit the strength of comparisons. These factors should be considered when interpreting the differences between our results and prior studies.

The control group was selected based on previously known conditions associated with endostatin levels. However, our results suggest that there may be other conditions, not yet studied, which could lead to an increase in endostatin levels.

Conclusions

We found that serum endostatin levels in COVID-19 infected patients during the acute phase in the emergency department were not elevated. This study suggests that serum endostatin levels are not a good predictor for lung involvement or mortality in COVID-19 patients in the emergency department. Further studies are needed to investigate endostatin levels in healthy individuals.

LIMITATIONS

This study has several limitations. First, although the total number of patients was adequate for primary comparisons, the control group was relatively small, which may have limited the power to detect subtle differences in endostatin levels. Second, serial measurements were not performed; therefore, we could not assess the dynamic behavior of endostatin during disease progression. Third, we included only COVID-19 patients without acute complications at the time of emergency department presentation. This selective inclusion may limit the generalizability of our findings to broader or more severe patient populations. Additionally, as a tertiary care hospital, our institution typically receives more complex cases, which may further affect external validity. Lastly, although multivariate analysis could have provided adjustment for potential confounders, the low number of ICU admissions and deaths made such analysis statistically unreliable and at high risk of overfitting. These aspects should be considered in future, large-scale, multicenter studies.

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