ORIGINAL RESEARCH

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Testican-1 as a Biomarker for Assessing Disease Severity in COVID-19 Patients

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Abstract

Objective: This study aimed to evaluate the levels of testican-1 in patients diagnosed with Coronavirus Disease-2019 (COVID-19) and to investigate its potential utility in predicting disease severity and clinical progression. Testican-1, a proteoglycan with known associations with sepsis and central nervous system damage, was hypothesized to serve as a biomarker for severe cases.

Materials and Methods: The study was conducted between September 15 and October 15, 2020, at University of Health Sciences Türkiye, Kayseri City Hospital, a designated pandemic center. A total of 89 patients with polymerase chain reaction-confirmed COVID-19 diagnoses were included. Patients were classified as moderate or severe based on clinical criteria. Serum testican-1 levels were measured using enzyme-linked immunosorbent assay. Routine biochemical parameters, C-reactive protein (CRP), procalcitonin, D-dimer, and other inflammatory markers, were analyzed.

Results: Testican-1 levels were significantly higher in patients with severe disease and admitted to intensive care units compared to moderate cases ($p<0.001$). However, no statistically significant correlations were found between testican-1 levels and other clinical markers, including CRP, procalcitonin, and D-dimer. A weak positive correlation with lactate levels and, and a weak negative correlation with basophil percentages.

Conclusion: Testican-1 shows promise as a specific biomarker for assessing the severity of COVID-19, potentially aiding clinicians in prognosis and management. While it does not correlate strongly with other inflammatory markers, its distinct association with severe disease underscores its utility.

Keywords: COVID-19, testican-1, biomarker, disease severity, clinical progression

Introduction

Coronavirus Disease 2019 (COVID-19), which is spreading rapidly around the world, has been declared a pandemic by the World Health Organization [1]; the first case was detected in Türkiye on March 11, 2020. The virus that causes COVID-19 is a member of the severe acute respiratory syndrome coronavirus virus family [2]. The disease can cause severe symptoms in humans, including cough, muscle aches, fever, severe shortness of breath, pneumonia, and sepsis [1].

Current information indicates that the disease is more severe in older people, men, and those with comorbidities [2,3]. The definitive diagnosis of the disease is the detection of the virus by real-time reverse transcriptase-polymerase chain reaction (PCR). However, the demonstration of diffuse lung involvement by computed tomography is also helpful in the diagnosis, especially in patients with or without contact [4].

Although there is no specific laboratory test to diagnose the disease, markers of infection and elevated levels of markers of thrombophilia, such as D-dimer, are present. COVID-19 is also known to cause cytokine storms, leading to conditions sepsis, multi-organ failure, and death [5].

Testican-1 is a proteoglycan carrying chondroitin sulfate and heparan sulfate chains and is originally identified as a precursor of glycosaminoglycan peptide in seminal plasma. It has been

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found to be particularly abundant in the thalamus and upregulated by astroglial cells in the brain [6]. Studies have shown that it can be detected in brain and central nervous system injury and sepsis [6-8].

In this study, we evaluated testican-1 levels along with various parameters in patients diagnosed with COVID-19. Thus, we attempted to determine the utility of testican-1 levels in predicting the clinical course and diagnosis of COVID-19 patients.

Materials and Methods

Study Setting and Population

This prospective study was conducted at University of Health Sciences Türkiye, Kayseri City Hospital between 15.09.2020 and 15.10.2020. Our hospital has been working as a pandemic hospital since March 2020. The study was conducted with the permission of the Ethics Committee of University of Health Sciences Türkiye, Kayseri City Hospital (decision number: 144, date: 03.09.2020). An informed consent form was obtained from all patients.

The patients included in the study were those who applied to the Emergency Department of University of Health Sciences Türkiye, Kayseri City Hospital and, after their first treatment, were admitted to the COVID-19 ward or intensive care units (ICU) with a preliminary diagnosis of COVID-19 after their first treatment. Patients were classified as moderate or severe according to their clinics. Clinically moderate patients were selected from those who were conscious, had oxygen saturation not falling below 85%, did not use assisted respiratory muscles, and were treated with ward follow-up. Patients considered severe were selected from patients who were followed up in the ICU, had an end-tidal oxygen saturation below 85%, were using assisted respiratory muscles, and were in poor general condition. Six patients deteriorated in their clinics during ward follow-up and were transferred to the ICU during the study. Therefore, the data of these patients were considered ward follow-up. The patients' PCR results were monitored, and patients who tested positive for COVID-19 were included in the study.

Data Collection

Testican-1 values were also examined in addition to the blood parameters taken during the routine follow-up of the patients. Blood samples were also obtained in the morning for testican-1 in PCR-positive patients. Routine biochemical parameters, C-reactive protein (CRP), and procalcitonin levels were determined using standard methods with an AutoAnalyzer (Cobas 8000, Roche Diagnostics, Indianapolis, IN, USA). D-dimer and complete blood count AutoAnalyzers (Diagnostica Stago, France and Sysmex XN 1000, Japan); Serum samples were separated after centrifugation at 5000 RPM (NF 400 centrifuge, Türkiye) for 10 minutes. Serum samples of patients were stored at -80 °C until tested. Serum testican-1 levels will be investigated by sandwich enzyme immunoassay using Human Testican-1 Enzyme Immunosorbent Test Kit; Range: 0.156-10 ng/mL, minimum detectable concentration: 0.061 ng/mL, USCN Business Co., Wuhan, China. The testican-1 level was analyzed according to the manufacturer's instructions and expressed in pg/mL. The concentrations of the samples were calculated using calibration curves obtained from operating standards at known levels. The intra-assay and inter-assay coefficient of variation were calculated as <10% for this analysis.

Statistical Analysis

To determine the number of samples in the study, the sample size was calculated using G-Power (3.1) version with a power of 0.80, taking the Lee et al. [6] study as an example and assuming an alpha of 0.05. Descriptive statistics were presented with frequency, percentage, mean, standard deviation, median, 25% quartile (Q1), and 75% quartile (Q3). The assumption of normality was checked using the Shapiro-Wilk test, Skewness and Kurtosis values, and q-q plots. The independent samples t-test (independent two-sample t-test) was used the Mann-Whitney U test was used. Spearman's Correlation test was used because the assumption of normality was not met in the relationship between numerical variables. P-values less than 0.05 were considered statistically significant. The analyses were performed with SPSS 23.0 software.

Results

Eighty nine patients were included in the study. The gender, age, general status, and parameter values of these patients are given in Table 1.

No statistically significant differences have been found between testican-1 concentration levels of women and men, in our study. Testican-1 concentration levels were found to be statistically significantly higher in patients hospitalized in intensive care and in patients with severe general conditions ($p<0.001$) (Table 2).

No statistically significant relationship was found between testican-1 concentration and age, ferritin, fibrinogen, D-dimer, CRP, procalcitonin, and sedimentation variables all patients and patients with moderate and severe conditions ($p>0.05$) (Table 3).

A statistically significant weak negative relationship was found with basophil percentage ($r=-0.226$; $p=0.033$), whereas a statistically significant weak positive relationship was found between testican-1 concentration and lactate in all patients ($r=0.218$; $p=0.041$) (Table 3).

Testican-1 concentration, age, ferritin, D-dimer, CRP, procalcitonin, lactate, white blood cells (WBC), neutrophil,

Table 1. Parameters of patients

		n	Percent	Mean (SD)	Median (Q1-Q3)
Gender	Female	37	42%		
	Male	52	58%		
Ward/intensive care unit	Ward	57	64%		
	ICU	32	36%		
Clinic status	Moderate	51	57%		
	Severe	38	43%		
Age		89			60 (90-74)
Testican-1 concentration (pg/mL)		89		2704.83 (2793.38)	1650 (11360-3480)
Ferritin (µg/L)		89		541.76 (710.18)	275 (4685-592)
Fibrinogen (mg/L)		89		5078.2 (1503.55)	5130 (9300-6160)
D-dimer (µg/L)		89		2291.91 (3724.15)	1110 (23390-2300)
C-reactive protein (mg/mL)		89		61.11 (71.04)	34 (332.5-86.7)
Procalcitonin (µg/L)		89		3.55 (16.32)	0.13 (100-0.32)
Sedimentation (mm/h)		89		49.84 (35.04)	43 (135-73)
Laktat (mmol/L)		89		1.25 (0.66)	1 (4.2-1.2)
White blood cells		89		7.91 (4.43)	6.99 (27.85-9.16)
Neutrophil%		89		65.03 (21.93)	68.2 (94.8-81.1)
Lymphocyte%		89		19.69 (13.1)	17.8 (52.4-29)
Monocyte%		89		7.6 (4.89)	7.5 (34.5-9.7)
Eizinophil%		89		1.3 (1.47)	0.8 (5.6-1.8)
Basophil%		89		0.7 (1.58)	0.3 (15-0.6)
Platelet		89		253.81 (96.88)	247 (600-299)

SD: Standard deviation, ICU: Intensive care unit

Table 2. Comparison of testican-1 concentration with gender, hospitalization, and clinic status (Mann-Whitney U test)

	Testican-1 concentration (pg/mL)	n	Mean (SD)	Median (Q1-Q3)	Test ist	p
Gender	Female	37	2530 (2831.86)	1440 (700-3200)	866.5	0.427
	Male	52	2829.23 (2786.62)	1705 (795-3940)		
Ward/ICU	Ward	57	1741.93 (1557.41)	1110 (580-2410)	454	**<0.001**
	ICU	32	4420 (3609.33)	3215 (1385-7500)		**<0.001**
Clinic status	Moderate	51	1660.59 (1490.33)	1100 (570-2410)	505.5	**<0.001**
	Severe	38	4106.32 (3469.39)	2835 (1330-6130)		**<0.001**

SD: Standard deviation, ICU: Intensive care unit

lymphocyte, monocyte, eosinophil, and basophil values were found to be statistically significantly higher in patients with a severe general condition compared to those with a moderate general condition ($p<0.05$). Fibrinogen, sedimentation, and platelet values were not found to be significant (Table 4).

Testican-1 concentration, age, D-dimer, CRP, procalcitonin, WBC, neutrophil, lymphocyte, and basophil were found to be statistically significantly higher in patients hospitalized in the ICU compared to those hospitalized in the ward ($p<0.05$) (Table 5).

Discussion

COVID-19, which surrounds the world, has become a test for health care systems. Each country has tried to implement its own treatment plans, although the World Health Organization has tried to establish a specific protocol. However, the

Table 3. Comparison of testican-1 concentration with age, ferritin, D-dimer, CRP, procalcitonin, sedimentation, lactate, WBC, NE%, LY%, MO%, EO%, BA%, and platelet (p<0.05, Spearman's correlation test)

Concentration		Age	Ferritin (µg/L)	Fibrinogen (mg/L)	D-dimer (µg/L)	CRP (mg/mL)	Procalcitonin (µg/L)	Sed (mm/h)	
All patient	r	0.098	0.193	0.166	0.174	0.161	0.168	0.141	
	p	0.362	0.07	0.121	0.104	0.131	0.116	0.187	
	n	89	89	89	89	89	89	89	
Moderate	r	0.14	0.235	0.117	0.106	0.058	-0.119	0.14	
	p	0.326	0.097	0.415	0.457	0.686	0.407	0.326	
	n	51	51	51	51	51	51	51	
Severe	r	0.038	-0.127	-0.103	-0.302	-0.133	-0.24	0.038	
	p	0.82	0.446	0.54	0.065	0.425	0.146	0.82	
	n	38	38	38	38	38	38	38	
Concentration		**Lactate (mmol/L)**	**WBC**	**NE%**	**LY%**	**MO%**	**EO%**	**BA%**	**Platelet**
All patient	r	0.218*	0.18	0.06	-0.142	-0.174	-0.1	-0.226*	-0.035
	p	0.041	0.091	0.574	0.185	0.103	0.351	0.033	0.748
	n	89	89	89	89	89	89	89	89
Moderate	r	0.204	0.12	-0.098	-0.033	-0.094	-0.042	-0.088	0.171
	p	0.15	0.401	0.495	0.818	0.511	0.77	0.541	0.229
	n	51	51	51	51	51	51	51	51
Severe	r	-0.072	-0.208	-0.205	0.181	0.015	0.018	-0.035	-0.149
	p	0.666	0.211	0.218	0.278	0.928	0.916	0.835	0.373
	n	38	38	38	38	38	38	38	38

* Correlation is significant at the 0.05 level (2-tailed). WBC: White blood cell, NE%: Neutrophil (%), LY%: Lymphocyte (%), MO%: Monocyte (%), EO%: Eosinophil (%), BA%: Basophil (%), CRP: C-reactive protein

increasing number of patients sometimes exceeded the capacity of the health systems and led to the hospitalization of patients depending on certain criteria. Clinical status, age, and comorbidities, and pulmonary imaging for diagnosis have been prioritized in emergency admissions in Türkiye and many other countries. Treatment has been designed according to the evaluation of PCR positivity [9]. It is known that patients' condition may deteriorate during treatment. In this case, we thought that an examination that could predict the patients' clinical outcomes was important, and we considered using testican-1, which has been shown to be useful in sepsis, although with a small number of publications, for this purpose.

In a study of 82 cases conducted by Lee et al. [6] a correlation was found between testican-1 levels of patients diagnosed with sepsis and the severity of the disease. In our study, we primarily compared testican-1 levels in patients admitted to the ward and ICU, and in patients classified as moderate and severe according to their clinical status. We found higher levels in ICU patients and patients with severe clinical status compared with patients admitted to the ward and those with moderate clinical status. We believe that the difference between these values is not only statistically significant but also important in terms of showing the severity of the disease. We believe that this difference in testican-1 levels may be helpful in assessing the severity of the disease or in clinical prediction in ward follow-up. Therefore, this increase in testican-1 levels may be a warning that the patients are approaching the onset of sepsis.

Wang et al. [10] showed WBC and neutrophil elevation, thrombocytopenia, basophil, eosinophil, and monocyte decrease, especially in patients with severe clinical conditions and ICU admission, similar to our study. Zhang et al. [11] found a relationship between procalcitonin levels and disease severity in their study. Similarly, in our results, procalcitonin levels increased with clinical deterioration. In our study, we did not find a statistical relationship between testican-1 concentrations and age, ferritin, fibrinogen, D-dimer, CRP, procalcitonin, and sedimentation regardless of clinic. However, we believe that this result is important in this way. The testican-1 level can be used to evaluate the severity of the disease, not to diagnose. This sentence is a fragment and requires additional context to form a complete sentence: in addition, there was a positive correlation between testican-1 and lactate level, and a negative correlation between

Table 4. Comparison of parameters according to disease severity

	Clinic status	n	Mean (SD)	Median (Q1-Q3)	Test ist	p
Age	Moderate	51	54.29 (16.67)	53 (43-65)	-4.676[a]	**<0.001**
	Severe	38	69.76 (13.6)	70 (63-78)		
Testican-1 concentration (pg/mL)	Moderate	51	1660.59 (1490.33)	1100 (570-2410)	505.5[b]	**<0.001**
	Severe	38	4106.32 (3469.39)	2835 (1330-6130)		
Ferritin (µg/L)	Moderate	51	378.88 (446.32)	223 (118-434)	681.5[b]	**0.017**
	Severe	38	760.37 (919.09)	425 (178-992)		
Fibrinogen/mg/L)	Moderate	51	4840.39 (1535.98)	4930 (3610-5820)	-1.749[a]	0.084
	Severe	38	5397.37 (1416.33)	5410 (4340-6330)		
D-dimer (µg/L)	Moderate	51	1321.96 (1855.65)	510 (290-1580)	504[b]	**<0.001**
	Severe	38	3593.68 (5029.51)	1810 (1110-3550)		
C-reactive protein (mg/mL)	Moderate	51	38.24 (51.78)	12 (2.8-69.1)	476.5[b]	**<0.001**
	Severe	38	91.8 (81.79)	68.65 (34-117.6)		
Procalcitonin (µg/L)	Moderate	51	0.22 (0.38)	0.06 (0.04-0.16)	467[b]	**<0.001**
	Severe	38	8.03 (24.44)	0.22 (0.13-0.98)		
Sedimentation (mm/h)	Moderate	51	44.39 (32.95)	40 (18-68)	765.5[b]	0.091
	Severe	38	57.16 (36.84)	56 (23-85)		
Lactate (mmol/L)	Moderate	51	1.06 (0.26)	1 (1-1)	547.5[b]	**<0.001**
	Severe	38	1.5 (0.9)	1.2 (1-1.8)		
White blood cells	Moderate	51	6.1 (2.18)	5.59 (4.43-7.44)	432.5[b]	**<0.001**
	Severe	38	10.32 (5.46)	8.73 (6.74-12.24)		
Neutrophil%	Moderate	51	57.91 (20.17)	61.2 (49.1-70.1)	424[b]	**<0.001**
	Severe	38	74.57 (20.75)	81.75 (68.5-88.3)		
Lymphocyte%	Moderate	51	24.92 (13.42)	22.9 (15.8-35.2)	439.5[b]	**<0.001**
	Severe	38	12.67 (8.74)	10.45 (6.6-15.9)		
Monocyte%	Moderate	51	8.51 (5.18)	8.2 (5.8-10.4)	675.5[b]	**0.015**
	Severe	38	6.37 (4.22)	5.25 (3.3-9.2)		
Eizinophil%	Moderate	51	1.52 (1.44)	1.2 (0.3-2.2)	715[b]	**0.035**
	Severe	38	1 (1.47)	0.4 (0.1-1.4)		
Basophil%	Moderate	51	0.78 (2.06)	0.4 (0.2-0.7)	577[b]	**0.001**
	Severe	38	0.28 (0.27)	0.2 (0.1-0.4)		
Platelet	Moderate	51	259.98 (88.45)	247 (198-311)	887[b]	0.496
	Severe	38	245.53 (107.83)	245.5 (175-294)		

[a]Independent two-sample t-test, [b]Mann-Whitney U test

SD: Standard deviation

testican-1 and basophil level. In particular, we believe that the relationship with lactate level supports our hypothesis that it could be a warning to the clinician when the disease changes direction towards sepsis. The negative correlation in basophil levels may also be related to the rate at which basophils change in sepsis.

It was found that those with severe disease in our study were of advanced age, similar to the studies by Guan et al. [12] and Zhou et al. [5]. D-dimer levels were found to be high in severe COVID-19 patients, and the mortality rate was higher in D-dimer-positive patients in the review by Shah et al. [13]. In our study, there was also a significant difference in age, D-dimer, CRP, procalcitonin, lactate, WBC, neutrophil, lymphocyte, basophil, and platelet levels between ICU patients and patients with poor general condition. This is also consistent with previous studies in COVID-19 patients.

In our study, there were no gender differences in testican-1 levels. However, the male sex was predominant in the patients. In our study, COVID-19 disease was seen at a high rate in males, similar to the study by Guan et al. [12].

Table 5. Comparison of patients hospitalized in intensive care unit according to ward patients

	Hospitalization	n	Mean (SD)	Median (Q1-Q3)	Test ist	p
Age	Ward	57	56.05 (17.05)	54 (45-69)	-3.818[a]	**<0.001**
	ICU	32	69.53 (13.83)	70 (60.5-77.5)		
Testican-1 concentration (pg/mL)	Ward	57	1741.93 (1557.41)	1110 (580-2410)	454[b]	**<0.001**
	ICU	32	4420 (3609.33)	3215 (1385-7500)		
Ferritin (µg/L)	Ward	57	501.11 (736.98)	245 (141-552)	793,5[b]	0.311
	ICU	32	614.19 (664.92)	307.5 (166.5-780.5)		
Fibrinogen/mg/L)	Ward	57	4933.33 (1519.11)	5030 (3860-5900)	-1.216[a]	0.227
	ICU	32	5336.25 (1463.33)	5260 (4255-6310)		
D-dimer (µg/L)	Ward	57	1634.21 (2529.45)	650 (310-1580)	566,5[b]	**0.003**
	ICU	32	3463.44 (5059.74)	1810 (865-3115)		
C-reactive protein (mg/mL)	Ward	57	43.02 (55.31)	20.5 (4.1-69.1)	501.5[b]	**<0.001**
	ICU	32	93.33 (84.41)	74.25 (33.5-123.9)		
Procalsitonin (µg/L)	Ward	57	1.98 (13.22)	0.08 (0.04-0.21)	522[b]	**0.001**
	ICU	32	6.35 (20.68)	0.2 (0.13-1.4)		
Sedimentation (mm/h)	Ward	57	47.49 (34)	42 (18-69)	816[b]	0.412
	ICU	32	54.03 (36.99)	52 (23-85.5)		
Lactate (mmol/L)	Ward	57	1.07 (0.3)	1 (1-1)	476.5[b]	**<0.001**
	ICU	32	1.57 (0.95)	1.2 (1-1.95)		
White blood cells	Ward	57	6.38 (2.79)	5.59 (4.43-7.49)	380[b]	**<0.001**
	ICU	32	10.62 (5.45)	8.97 (7.28-12.59)		
Neutrophil%	Ward	57	57.95 (23.05)	62.5 (49.1-72.9)	399[b]	**<0.001**
	ICU	32	77.64 (12.19)	81.75 (69.55-88.25)		
Lymphocyte%	Ward	57	22.89 (14.13)	22.4 (13.9-33.3)	567.5[b]	**0.003**
	ICU	32	13.97 (8.6)	11.65 (7.55-19.25)		
Monocyte%	Ward	57	7.99 (5.34)	8 (5.4-10.2)	766[b]	0.212
	ICU	32	6.9 (3.94)	5.65 (4.3-9.4)		
Eizinophil%	Ward	57	1.37 (1.42)	1 (0.14-2)	805.5[b]	0.361
	ICU	32	1.16 (1.55)	0.55 (0.1-1.55)		
Basophil%	Ward	57	0.72 (1.96)	0.4 (0.2-0.7)	640.5[b]	**0.019**
	ICU	32	0.3 (0.28)	0.2 (0.1-0.45)		
Platelet	Ward	57	258.65 (86.72)	254 (198-305)	814.5[b]	0.404
	ICU	32	245.19 (113.74)	74.5-292.5)		

[a]Independent two-sample t-test, [b]Mann-Whitney U test

SD: Standard deviation, ICU: Intensive care unit

When the correlation between all these values and testican-1 values is examined, we think that the testican-1 level will be useful in predicting the severity of the disease.

Study Limitations

In addition, it is necessary to mention some of our limitations. Our study was conducted on inpatients and patients diagnosed with the disease. Evaluating using a control group without any disease may be significant to determine at least one significant cut-off value.The study was conducted at a single centre (Kayseri City Hospital), which may limit the generalisability of the results to other patient populations or different geographical regions. The sample size of 89 patients is relatively small. This may affect statistical power and limit the ability to detect meaningful differences, particularly in subgroup analyses.

Conclusion

COVID-19 continues to spread and kill all over the world. Prevention and reduction of the spread of this disease are as important as its treatment. The decision of which patients will be hospitalized or taken under outpatient treatment is left to the clinician's experience together with the patient's clinical results. We believe that the testican-1 level is a test that will help the clinician in this case. We hope that our study will pave the way for further studies on this subject in the future.

Ethics

Ethics Committee Approval: The study was conducted with the permission of the Ethics Committee of University of Health Sciences Türkiye, Kayseri City Hospital (decision number: 144, date: 03.09.2020).

Informed Consent: An informed consent form was obtained from all patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: O.B., Concept: O.B., D.K., Design: O.B., Data Collection or Processing: O.B., Analysis or Interpretation: O.B., Literature Search: O.B., D.K., Writing: O.B., D.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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