Clin. Lab. 2026;72:XXX-XXX

ORIGINAL ARTICLE

The Role of VEGF-A in Young Patients with Acute Coronary Syndrome

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SUMMARY

Background: **The objective of the present study was to examine the correlation between acute coronary syndrome (ACS) and vascular endothelial growth factor A (VEGF-A) in young adult patients (aged 18 - 50 years).**
Methods: **In this single-center cross-sectional study, 44 young patients diagnosed with ACS were compared with 44 healthy controls with a similar age and gender distribution. Serum levels of VEGF-A were measured by enzyme-linked immunosorbent assay (ELISA) in blood samples obtained at the time of presentation to the emergency department.**
Results: **Out of the 44 patients included in the study with a diagnosis of ACS, 10 (22.7%) were diagnosed with unstable angina pectoris, 11 (25%) with non-ST-elevation myocardial infarction, and 23 (52.2%) with ST-elevation myocardial infarction (STEMI). Out of the patients diagnosed with STEMI, 13 (29.5%) were classified as inferior STEMI, while 10 (22.7%) were categorized as anterior STEMI. No statistically significant differences were observed between the patient and control groups regarding age, gender, and comorbidities ($p > 0.05$ for each). The mean serum VEGF-A value of the patient group was 364.19 ± 151.51. The mean serum VEGF-A value of the control group was 538.41 ± 559.70. The serum value of the patient group for VEGF-A was lower than that of the control group, but this difference was statistically nonsignificant ($p = 0.052$). The creatinine and C-reactive protein (CRP) values of the patient group were found to be significantly higher than those of the control group ($p = 0.022$ and $p = 0.010$, respectively).**
Conclusions: **Serum levels of VEGF-A were found to be lower in young patients with ACS compared to the control group, although this difference was statisti-cally nonsignificant. This finding implies a relationship between low levels of VEGF-A and an increased risk of ACS in young individuals.**
(Clin. Lab. 2026;72:xx-xx. DOI: 10.7754/Clin.Lab.2025.250555)

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Manuscript accepted June 2, 2025

KEYWORDS

acute coronary syndrome, VEGF-A, young ACS, USAP, NSTEMI, STEMI

INTRODUCTION

Cardiovascular disease is the foremost cause of mortality on a global scale, with ischemic heart disease accounting for nearly 50% of these fatalities [1]. Acute coronary syndrome (ACS) covers the following: unstable angina pectoris (USAP), ST elevation myocardial

infarction (STEMI), and non-ST elevation myocardial infarction (NSTEMI). The diagnosis of ACS is based on clinical signs, electrocardiogram (ECG) findings, and biochemical evidence of myocar-dial damage [2].

It has been reported that there has been an increased incidence of ACS in young adult patients [3]. As demonstrated by the existing data, young patients constitute between 0.4% and 19% of all ACS cases [4]. The most prevalent risk factors for ACS in young adult patients include smoking, obesity, hyperlipidemia, and coronary artery disease (CAD), as well as a family history of cardiovascular disease [5]. Vascular endothelial growth factor A (VEGF-A) is a signaling protein that is the first member of the VEGF protein family. VEGF-A performs several functions, including proangiogenic activity, vascular permeability activity, and stimulation of cell migration in both macrophage-derived cells and endothelial cells [6]. It is demonstrated to be responsible for a wide range of physiological and pathological processes, including cardiovascular diseases. VEGF-A promotes myocardial angiogenesis in acute coronary syndrome by way of secretion through inflammation, hypoxia, mechanical stress, and cellular signaling pathways. Nonetheless, elevated levels of VEGF-A have the potential to engender an augmentation in cardiovascular risks, a phenomenon that is attributed to the stimulation of plaque growth and subsequent destabilization [7].

It has been documented that serum levels of VEGF-A exhibit an increase in patients diagnosed with CAD [8]. However, to the best of our knowledge, no study has examined VEGF-A levels in young adult ACS patients. The objective of this study was to elucidate the correlation between ACS and VEGF-A in young adult patients.

MATERIALS AND METHODS

Study design and ethics committee approval

The present study was designed as a single-center cross-sectional study in a secondary state hospital. Following the requisite approval from the local ethics committee (protocol number: SUKAEK-2022 12/26, date: 11-23-2022), the study was conducted with ACS patients admitted to the emergency department between 12-31-2022 and 12-31-2023 and healthy volunteers with similar sociodemographic characteristics.

Patient selection

Patients over 18 and under 50 years of age who had been diagnosed with ACS and for whom this diagnosis had been confirmed by clinical, laboratory, and imaging methods were included in the study. Informed consent was provided by the patients themselves or their guardians. Patients with a history of cardiac pathologies such as ACS, heart failure, valvular diseases, structural heart diseases, collagen tissue diseases (rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, etc.) who were younger than 18 and older than 50 years of age and whose informed consent could not be obtained were excluded from the study.

Formation of the control group and collection of data

A control group was established from healthy volunteers who exhibited demographic characteristics analogous to those of the patients and who did not satisfy any of the exclusion criteria, with their consent being obtained.

The data collection form encompassed a range of sociodemographic characteristics, vital signs, comorbid diseases, and laboratory results (blood gas, biochemistry, hemogram).

Collection of samples

Blood samples were collected from the patients and control groups at the time of admission to the emergency department without interruption to the standard treatment protocol. Samples were obtained by means of a 5 mL whole blood hemogram tube, which was then subjected to a centrifugation process at 5,000 rpm for 5 minutes. The serum samples were stored at -80°C until the commencement of the study. The levels of VEGF-A were deter-mined by enzyme-linked immunosorbent assay (ELISA) using an Allsheng AMR-100 ELISA microplate reader. The results were meticulously documented on the designated data collection form.

Treatment management of patients

Patients diagnosed with ACS were treated in accordance with the consensus guidelines specified in Reference 9. All ACS patients received appropriate antiplatelet and anticoagulant therapy in the emergency department. Patients diagnosed with STEMI were treated with primary coronary intervention (PCI). Patients diagnosed with NSTEMI and exhibiting hemodynamic instability, persistent pain refractory to medical therapy, acute heart failure, mechanical complications, and dynamic ECG changes were treated with early invasive treatment. Patients were hospitalized for follow-up and treatment by a cardiologist who was not involved in the study.

Statistical analysis

The collected data were analyzed on a computer using IBM SPSS (version 25) and MedCalc (version 20; MedCalc Software Ltd., Ostend, Belgium) software programs. The analyses were conducted at 95% confidence level. In order to determine the most appropriate analysis method for numerical data, the Kolmogorov-Smirnov test results were examined in order to ascertain whether the data were normally distributed. The descriptive statistics expressed as mean and standard deviation were utilized for normally distributed numerical data, whilst the median (minimum - maximum) was employed for non-normally distributed data. Finally, number (n) and percentage (%) were used for nominal data. In paired group comparisons, Student´s *t*-test was employed to compare numerical data that conformed to a

normal distribution, while the Mann-Whitney U test was utilized for data that did not adhere to a normal distribution. Categorical data was compared using either the chi-squared test or Fisher's exact test. For all comparisons, values of $p < 0.05$ were considered to be statistically significant.

RESULTS

During the specified period, 76 patients were admitted to the emergency department suffering from ACS. A total of 32 patients who met at least one of the exclusion criteria were excluded from the study. A patient group was established, with 44 patients included in the study. A control group was established, comprising 44 volunteers who exhibited demographic characteristics analogous to those of the patient group. The flowchart illustrating the study's methodology is presented in Figure 1. Out of the 44 patients included in the study with a diagnosis of ACS, 10 (22.7%) were diagnosed with USAP, 11 (25%) with NSTEMI, and 23 (52.2%) with STEMI (Figure 1). Out of the patients diagnosed with STEMI, 13 (29.5%) were classified as inferior STEMI, while 10 (22.7%) were categorized as anterior STEMI.

The clinical characteristics of the patient and control groups are presented in Table 1. No statistically significant differences were observed between the patient and control groups regarding age, gender, and comorbidities ($p > 0.05$ for each). The systolic blood pressure of the patient group was found to be higher than that of the control group ($p = 0.040$). The investigation revealed that diastolic blood pressure and mean arterial pressure were similar in both groups ($p > 0.05$ for each).

The median EF value of the patient group was 58% (35 - 65). The median EF of the control group was 62% (46 - 67). The EF of the patient group was lower than that of the control group ($p < 0.001$) (Table 1).

The laboratory findings of the patient and control groups are presented in Table 2. Consequently, creatinine and CRP values of the patient group were found to be significantly higher than those of the control group ($p < 0.05$ for each).

The mean serum VEGF-A value of the patient group was 364.19 ± 151.51. The mean serum VEGF-A value of the control group was 538.41 ± 559.70. The serum value of the patient group for VEGF-A was lower than that of the control group, but this difference was statistically nonsignificant ($p = 0.052$).

DISCUSSION

The findings of our study demonstrated that serum levels of VEGF-A were reduced in young patients with acute coronary syndrome (ACS) in comparison to the control group, although this difference was statistically nonsignificant. The relationship between serum levels of VEGF-A and ACS remains unclear from the existing literature. Despite the plethora of studies that have documented an augmentation in se-rum VEGF-A levels in ACS patients, it has concomitantly been reported that diminished serum VEGF-A levels exhibit a concomitant increase in arterial and ve-nous thromboembolic events (source). To the best of our knowledge, there is an absence of research in the literature investigating serum VEGF-A levels in young ACS patients. In this respect, the present study made significant contributions to the existing literature.

VEGF-A identified as a key regulator of vascular permeability and angiogenesis [10]. Furthermore, it influences hematopoiesis and the behaviour of white blood cells [11]. It has been demonstrated that within the nervous system, VEGF-A exerts a direct regulatory influence on neuronal migration and axon guidance, irrespective of its function in vascular structures [12]. Furthermore, it has been hypothesized that VEGF-A may exert a variety of functions in pathological conditions, including cancer and neurodegeneration [13]. VEGF-A has also been demonstrated to have a role in the pathophysiology of ischemic heart disease, coronary artery disease, and atherosclerosis [7].

VEGF-A plays a critical role in the physiological and pathophysiological processes of the cardiovascular system. In conditions of hypoxia, such as myocardial ischemia, there is an increase in the expression of VEGF-A through the process of hypoxia-induced HIF-1α (hypoxia-inducible factor-1α). This increase is instrumental in the process of reperfusion by triggering the process of angiogenesis in ischemic tissues [14]. In endothelial cells, the primary target of VEGF-A, activation of the vascular endothelial growth factor receptor 2 (VEGFR-2) stimulates the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) and mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathways, leading to endothelial proliferation, migration, and new capillary formation [15]. In cardiac tissue, the influence of VEGF-A on signaling is such that it exerts an indirect effect on the inhibition of cardiomyocyte apoptosis and promotion of cellular survival [16]. Consequently, VEGF-A is emerging as a significant therapeutic target in the context of vascular remodelling, as well as in the stimulation of cardiac regeneration. Furthermore, an increase in the levels of VEGF-A has been identified in the plasma following myocardial infarction, with these levels correlating with elevated concentrations of inflammatory cytokines [17]. This finding indicates that elevated levels of VEGF-A are associated with ongoing inflammatory activity and angiogenesis.

In addition to its role in angiogenesis, VEGF-A is a critical mediator for endothelial cell survival, normal function, and maintenance of vascular integrity [18]. Healthy vascular endothelium actively provides an antithrombotic surface and inhibits coagulation through the action of molecules such as nitric oxide (NO) and prostacyclin (PGI2). A reduction in vascular endothelial growth factor (VEGF) levels may induce endothelial

Table1. Clinical characteristics and vital findings of patient and control groups.

Features/Variables		Patient group (n = 44)	Control group (n = 44)	p-value
Age (years), mean ± SD		46.34 ± 2.50	46.02 ± 3.78	0.643
Gender, n (%)	female	14 (31.8)	21 (47.7)	0.127
	male	30 (68.2)	23 (52.3)	
Comorbidities, n (%)	DM	4 (4.5)	3 (3.4)	1.000
	HT	11 (25)	6 (13.6)	0.177
	cigarette use	6 (13.6)	8 (18.2)	0.560
SBP (mmHg), median (min - max)		130 (90 - 170)	130 (110 - 146)	0.040
DBP (mmHg), median (min - max)		75.50 (60 - 100)	74.50 (60 - 87)	0.239
MAP (mmHg), median (min - max)		93.33 (70 - 123.33)	93.50 (76.67 - 106.67)	0.208
BMI ($kg/m^{2)}$, mean ± SD		27.61 ± 2.31	26.46 ± 3.24	0.057
LVEF (%), median (min - max)		58 (35 - 65)	62 (40 - 67)	< 0.001

SBP systolic blood pressure, DBP diastolic blood pressure, MAP mean arterial pressure, BMI body mass index, LVEF left ventricular ejection fraction.

Table 2. Laboratory findings of patient and control groups.

Variables, mean ± SD	Patient group (n = 44)	Control group (n = 44)	p-value
Total cholesterol (mg/dL)	170.03 ± 29.03	159.89 ± 33.16	0.131
HDL (mg/dL)	40.24 ± 6.79	43.17 ± 9.78	0.106
LDL (mg/dL)	113.70 ± 29.71	106.64 ± 23.90	0.229
Triglycerides (mg/dL)	223.45 ± 158.46	174.80 ± 136.18	0.146
Urea (mg/dL)	28.50 ± 7.88	31.20 ± 10.41	0.173
Creatinine (mg/dL)	0.85 ± 0.14	0.77 ± 0.17	0.022
AST (U/L)	44.11 ± 32.43	36.22 ± 48.64	0.373
ALT (U/L)	44.01 ± 48.38	36.76 ± 52.75	0.503
Sodium (mmol/L)	138.93 ± 4.56	138.69 ± 2.28	0.753
Potassium (mmol/L)	4.29 ± 0.46	4.23 ± 0.38	0.521
CRP (mg/dL)	5.53 ± 2.89	3.70 ± 3.62	0.010
VEGF-A (pg/mL)	364.19 ± 151.51	538.41 ± 559.70	0.052

HDL high-density lipoprotein, LDL low-density lipoprotein, AST aspartate animotransferase, ALT alanine aminotransferase, CRP C-reactive protein, VEGF-A vascular endothelial growth factor A.

dysfunction, consequently attenuating the protective mechanisms that are instigated [19]. It is known that VEGF-A can stimulate endothelial nitric oxide synthase (eNOS) expression in the context of normal conditions [20]. Consequently, reduced levels of VEGF may result in diminished NO production. Endothelial dysfunction is also characterized by an increased expression of procoagulant factors, such as tissue factor, and a surface shift to a proinflammatory and prothrombotic phenotype [19]. The clinical implications of these changes are twofold. Firstly, there is an increased risk of arterial and venous thromboembolic events observed in patients receiving therapies that inhibit VEGF signaling [21,22]. Consequently, insufficient levels of VEGF-A may be considered a significant contributing factor to the pathogenesis of thrombosis by disrupting endothelial homeostasis.

A number of studies have previously reported the finding that serum levels of VEGF-A are increased in cases of acute coronary syndromes [23-25]. The study by Huang et al. demonstrated that serum levels of VEGF-A were elevated in patients with CAD in comparison to

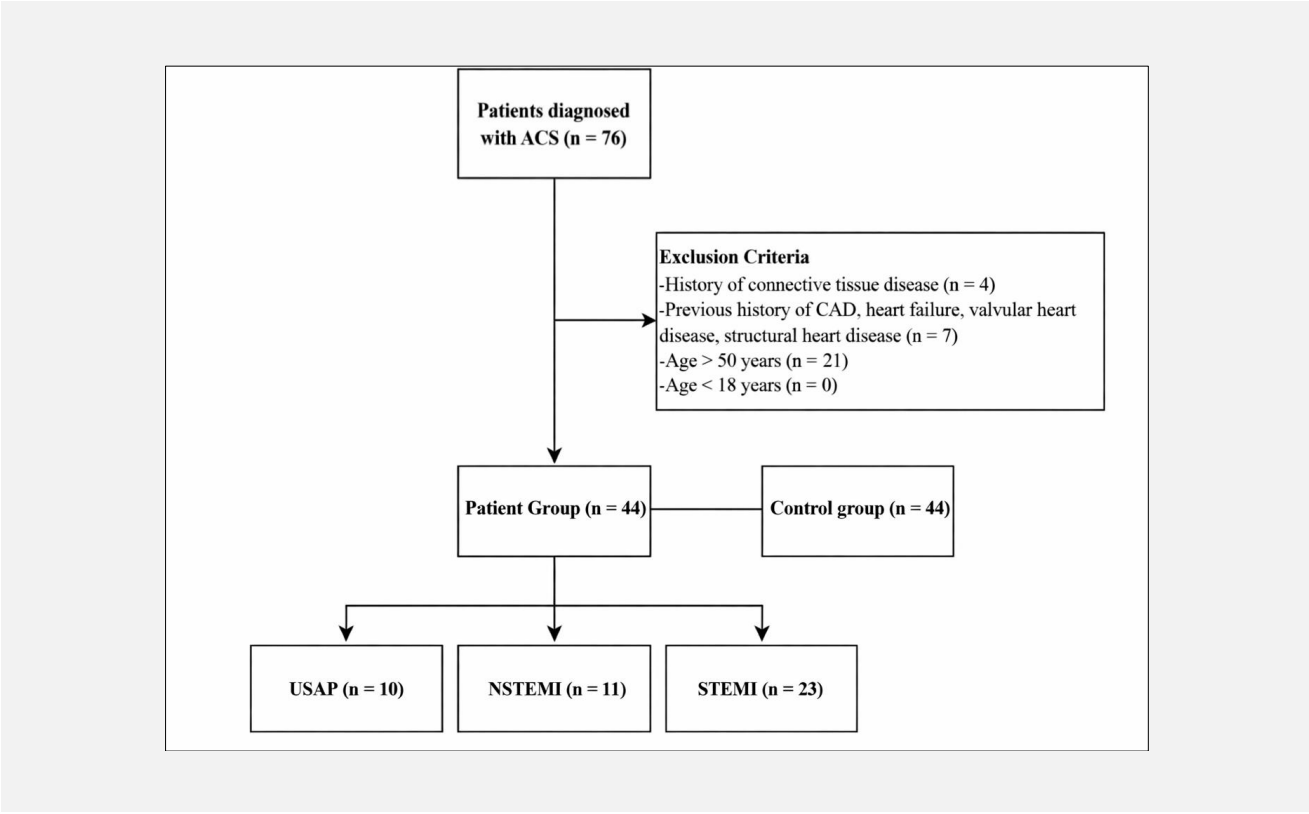

Figure 1. Study flow chart.

ACS acute coronary syndrome, CAD coronary artery disease, USAP unstable angina pectoris, NSTEMI non-ST-elevation myocardial ınfarction, STEMI ST-elevation myocardial ınfarction.

healthy volunteers and patients with stable angina pectoris [24]. In the study by Küçükturali et al., although serum VEGF-A levels were higher in patients with CAD and critical lesions (more than 70% stenosis in at least one of the three major coronary arteries) compared to the control group, no significant difference was found between patients with CAD and non-critical lesions (40% - 70% stenosis in at least one of the three major coronary arteries) and the control group [25]. In contrast to the findings reported in the existing literature, our study revealed that there was no statistically significant difference between the serum VEGF-A levels of ACS patients and healthy volunteers. However, the measured serum VEGF-A levels were found to be lower in the ACS patients. It is hypothesized that the observed findings are indicative of a relationship between low levels of VEGF-A and an elevated risk of thrombosis. However, the mechanism of our findings cannot be fully explained.

Limitations

The limitations of the present study are threefold. Firstly, it was single-centered. Secondly, the number of patients was relatively small. Thirdly, repeated serum VEGF-A measurements could not be performed. Moreover, the absence of investigation into the relationship between thrombosis burden and serum VEGF-A levels in patients constitutes another significant limitation.

CONCLUSION

Despite the absence of statistical significance in young ACS patients in comparison to the control group, low serum levels of VEGF-A were identified. This finding implies a relationship between low levels of VEGF-A and an increased risk of ACS in young individuals. Future studies that eliminate our limitations are needed in order to support our findings.

Ethical Approval Statement:

This study was approved by the local ethics committee (protocol number: SUKAEK-2022 12/26, date: 11-23-2022).

Source of Funds:

The authors received no financial support for the research, authorship, and/or publication of this article.

Declaration of Interest:
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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