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## LACK OF ASSOCIATION BETWEEN SERUM IL-25 LEVELS AND ACUTE CORONARY SYNDROME: A PRELIMINARY STUDY

<i>Purpose</i>	Here, for the first time, the possible association between IL-25 and the risk of acute coronary syndrome (ACS) in Iranian patients was investigated.
<i>Material and methods</i>	In this study, serum IL-25 concentrations were measured with an enzyme-linked immunosorbent assay in 88 ACS patients, 40 stable angina pectoris (SAP) patients, and 50 healthy control subjects.
<i>Results</i>	No significant differences in IL-25 concentrations were observed between SAP (340±168 ng/l), ACS (330±151 ng/l), and control (302±135 ng/l) groups (p=0.5), nor was there a difference among patients with 1, 2, or 3 vessel disease in the SAP and ACS groups. Linear regression analyses revealed that IL-25 was not correlated with coronary artery disease risk factors. Biochemical and demographic variables did not differ significantly among IL-25 quartiles.
<i>Conclusion</i>	Despite previous murine and human studies showing a protective role of IL-25 in atherosclerosis, our results revealed that IL-25 does not have potential implications for atherosclerosis development and management in humans.
<i>Keywords</i>	Acute coronary syndrome; acute myocardial infarction; IL-25; stable angina pectoris; unstable angina pectoris
<i>For citation</i>	Nadereh Naderi, Narges Farshidi, Hossein Farshidi, Hossein Montazerghaem, Mahsa Rahimzadeh. Lack of association between serum IL-25 levels and acute coronary syndrome: a preliminary study. <i>Kardiologiia</i> . 2021;61(4):60–65. [Russian: Надерен Надера, Наргес Фаршиди, Хоссейн Фаршиди, Хоссейн Монтазергхем, Манса Рахимзаден. Отсутствие связи между уровнем интерлейкина-25 в сыворотке крови и острым коронарным синдромом: предварительное исследование. <i>Кардиология</i> . 2021;61(4):60–65]
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### Introduction

Atherosclerosis, the primary cause of cardiovascular disease (CVD), is regarded as a chronic inflammatory disease of the arterial wall [1, 2]. New advances in the pathogenesis of atherosclerosis have provided evidence for a complex interaction between innate, adaptive immune cells and cytokines. Several recent studies on atherosclerosis revealed that cytokines act as a double-edged sword, which can either exacerbate the disease or protect against its development. T helper (Th) 1 and Th17-related cytokines, including IFN- $\gamma$  and IL-17 A, exert pro-atherogenic activity. Th<sup>2</sup> and regulatory T cell-related cytokines, including interleukin-5 and transforming growth factor- $\beta$ , have anti-atherogenic effects [3]. Recently, the cytokine interleukin-25 (IL-25) has been implicated in protection against atherosclerosis [4]. IL-25 belongs to the IL-17 cytokine family, produced by many cell types including T cells, group 2 innate lymphoid cells (ILC2s), dendritic cells and macrophages [5]. The role of the IL-17 family in acute coronary syndrome (ACS) has

been reported previously [6, 7]. Zhang et al. proved that IL-17A could dramatically enhance platelet activation and aggregation in ACS patients through the ERK2 signaling pathway, and it may provide a novel target for reducing the formation of atherothrombosis in coronary heart disease [8].

Interleukin-25 (IL-25), unlike other members of its family, promotes Th<sup>2</sup> [9], Th9 [10] and ILC2s responses [11] and plays a critical role in the development of allergy and asthma [12]. IL-25 negatively regulates the development of Th17-mediated autoimmune diseases [13]. It has been implicated in the protection against experimental autoimmune encephalomyelitis, rheumatoid arthritis [14], inflammatory bowel disease [15], experimental colitis [16], autoimmune diabetes [17], and atherosclerosis [4]. Anti-atherogenic effects of IL-25 has recently been described in murine models. Mantani et al. showed that IL-25 treatment of apoE-deficient mice (ApoE<sup>-/-</sup>) inhibits development of atherosclerosis. They also evaluated the effects of complete IL-25 deficiency on atherosclerosis

development in Apoe<sup>-/-</sup> mice. They found that Apoe<sup>-/-</sup> /IL-25<sup>-/-</sup> mice had more Th1 cells and interferon-gamma (INF-gamma) in the spleen, more IL-17 in plasma and increased atherosclerotic plaque formation in the aortic arch [18].

Based on the aforementioned studies showing IL-25's critical role in the progression of atherosclerosis in mice, assessing the functional properties of IL-25 has become an emerging aim in clinical cardiovascular disease. Nevertheless, the clinical significance of IL-25 in coronary artery disease (CAD) remains an unanswered question. The purpose of this study was to evaluate, for the first time, the serum concentration of IL-25 in patients with established atherosclerotic CHD as compared to that of healthy subjects and also to assess the potential association of IL-25 with the risk of ACS in Iranian patients. Additionally, the association between plasma IL-25 concentrations and various ACS risk factors were evaluated.

## Material and Methods

### Study subjects

This cross-sectional study was conducted on 50 healthy volunteers and 128 patients admitted for diagnostic coronary angiography in the Jorjani heart center at Bandar Abbas, Iran, between March 2018 and March 2019. The patients were categorized into two groups based on the Canadian Cardiovascular Society Classification System: a stable angina pectoris (SAP) group (n=40) and an acute coronary syndrome (ACS) group (n=88). The SAP patients were in class 1 or 2 of the Canadian Cardiovascular Society Classification System [19]. The ACS patients had unstable angina, non-ST-elevation (STE) MI, or STEMI. These patients presented to the emergency room with chest discomfort, and an electrocardiogram (ECG) and troponin measurement were performed. Unstable angina pectoris (UAP) was classified as Canadian Cardiovascular Society class 3 or 4 with ischemic discomfort, without electrocardiographic ST-segment elevation or elevation of troponin. Acute myocardial infarction (AMI), was identified by elevation of troponin and ischemic discomfort, with or without ST-segment elevation on the ECG. The group of healthy volunteers displayed no history or clinical signs of cardiovascular disease or biochemical coronary risk factors. Written informed consent was obtained from all patients and healthy subjects. The ethical committee of the Hormozgan University of Medical Sciences approved the study protocol (reference number: IR.HUMS.REC.1397.008). Patients were excluded if any of the following criteria were observed:

- 1) infectious and autoimmune diseases and receiving drugs that affect the immune system drugs;
- 2) history of thyroid, liver, kidney, and brain dysfunction;
- 3) valvular heart disease;

4) any type of malignancy.

Blood pressure and smoking were recorded. Smoking was defined as the use of >1 cigarettes/day at the time of recording. Weight (kg) divided by height squared (m<sup>2</sup>) is reported as body mass index (BMI). The waist circumference was measured at the level of the umbilicus. The mean value of three measurements was used for analysis.

### Sample collections and measurements

After admission, venous blood was collected from fasting patients and control subjects. The blood clot was centrifuged at 2500 g for 10 min at 4 °C (sigma 2-16KL), and the serum samples were stored at -70 °C for subsequent analysis. Total cholesterol, triglycerides, low and high-density lipoproteins, cholesterol, and blood glucose were analyzed in a biochemical autoanalyzer (Hitachi 7600, Japan). IL-25 serum concentration was measured using an enzyme-linked immunosorbent assay (ELISA) kit (Zell bio, Germany) according to the manufacturer's instructions. IL-25 concentration was calculated based on a standard curve developed over a linear range of the IL-25 standard solution. The sensitivity of the kit was (25 ng/l). The intra and inter assay variations were <10%.

### Coronary angiography and Gensini score

The Judkins technique was used to perform coronary angiography with a femoral approach. Results were interpreted by two blinded cardiologists. The diameter of the severe part of the lesion was measured. A 50% or more stenosis in at least one coronary vessel was accepted as coronary stenosis. To assess the severity of the disease, the Gensini score was calculated as defined previously [20].

### Statistical analyses

All statistical analyses were performed with the Statistical Package for Social Sciences, version 20.0 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test and homogeneity of variances were used for evaluating the normality of distributions. Data are presented as mean±SD if normally distributed and as median and interquartile range if non-normally distributed. One-way ANOVA was used for comparing demographic and clinical data between the SAP, ACS and control groups. Categorical variables were compared with a chi-square test and displayed as numerical and percentage values. Serum IL-25 concentrations and metabolic risk factors were analyzed with general linear regression analysis, and standardized regression coefficients are reported. Quantitative demographic and clinical data were compared between IL-25 quartiles using a one-factor ANOVA and are presented as mean±SD or as percentage. The Open Source Epidemiologic Statistics for Public Health software

**Table 1. Patient's demographic and clinical characteristics**

Variables	SAP (n=40)	ACS (n=88)	Control (n=50)	p, value
Age (years)	61.3±9.1	59.9±12.5	45.6±11.1	<0.0001
Sex (%)				
Male (n= 80)	47.5	46.6	36	0.4
Female (n=98)	52.5	53.4	64	
BMI <sup>1</sup> (kg/m <sup>2</sup> )	25±3.7	25±4.3	26±4.3	0.4
Waist (cm)	89.3±13	91.3±14.9	84.1±15.9	0.005
Systolic blood pressure (mmHg)	138.2±20.8	135.9±23.1	127.7±9.4	0.01
Diastolic blood pressure (mmHg)	81±16	84±14.0	77±5	0.3
LDL <sup>2</sup> cholesterol (mg/dl)	86±27	103±96	118±42	0.1
HDL <sup>3</sup> cholesterol (mg/dl)	44.1±11.1	41.9±10.6	46.7±15.5	0.03
Total cholesterol (mg/dl)	150.9±36.5	157±45.4	183.7±40.2	<0.0001
Triglycerides (mg/dl)	125.5±59.2	127.8±76.9	93.6±33.7	0.003
FBS <sup>4</sup> (mg/dl)	131±44	129.9±56.8	98.2±25.6	<0.0001
Smoking (%)	10.8	25	14.3	0.01
LVEF <sup>5</sup> (%)	50±15	46±10	–	0.2
Gensini score	32.4±35.1	62.3±50.6	–	<0.0001
IL-25 (ng/l)	340±168	330±151	302±135	0.5
Medical treatment (%)				
Aspirin	65.2	50.4	–	0.003
Beta-blocker	32.3	27.5	–	0.7
ACEI <sup>6</sup>	10.4	11.3	–	0.9
Statin	46.7	30.3	–	0.02
Nitrate	51.6	30.9	–	0.001
CCB <sup>7</sup>	12.6	7.3	–	0.2

Data are mean±SD or percentage. BMI<sup>1</sup>, body mass index; LDL<sup>2</sup>, low density lipoprotein; HDL<sup>3</sup>, high density lipoprotein; FBS<sup>4</sup>, fasting blood sugar; LVEF<sup>5</sup>, left ventricular ejection fraction; ACEI<sup>6</sup>, angiotensin-converting enzyme inhibitor; CCB<sup>7</sup>, Calcium channel blocker.

version 3.01 was used to estimate the required sample size to get 80% power of the study. Results were considered statistically significant at two-sided  $p < 0.05$ .

## Results

### Clinical and demographic characteristics of study population

Clinical and demographic characteristics of the SAP, ACS, and healthy controls are shown in Table 1. In this study, 80 men and 98 women were enrolled. There was no significant difference in gender distribution among the groups. The mean age of the SAP, ACS, and control groups were 61.3±9.1, 59.9±12.5 ( $p=0.7$ ), and 45.6±11.1 years, respectively ( $p < 0.0001$ ). Waist, systolic blood pressure, high density lipoprotein (HDL) cholesterol, total cholesterol, triglycerides, fasting blood sugar (FBS) and smoking differed significantly among the groups ( $p < 0.05$ ). There were no significant differences between BMI, diastolic blood pressure, and low density lipoprotein (LDL) cholesterol for the SAP, ACS, and control groups ( $p \geq 0.05$ ).

### IL-25 serum level in study subjects

As shown in Table 1, IL-25 serum concentrations were similar among the control, SAP and ACS groups ( $p=0.5$ ).

**Table 2. Association of serum IL-25 and cardiovascular risk factors as assessed with multivariable regression analysis**

Multivariate analysis		
Variable	$\beta$ coefficient	p value
Stable angina pectoris		
Age	-0.1	0.7
Gender	-0.1	0.6
BMI	0.1	0.7
Waist	-0.2	0.5
HDL cholesterol	0.6	0.1
LDL cholesterol	0.7	0.3
Triglycerides	0.4	0.3
Total cholesterol	-0.9	0.2
FBS	0.2	0.4
Gensini score	0.03	0.9
Acute coronary syndrome		
Age	0.1	0.6
Gender	-0.1	0.6
BMI	0.2	0.2
Waist	-0.2	0.1
HDL cholesterol	0.05	0.7
LDL cholesterol	-0.1	0.3
Triglyceride	0.2	0.1
Total cholesterol	0.1	0.3
FBS	0.1	0.4
Gensini score	-0.05	0.7

## Correlations between IL-25

### serum level and cardiovascular risk factors

To assess the correlation between IL-25 and risk factors for coronary artery disease, including BMI, LDL cholesterol, HDL cholesterol, total cholesterol, triglyceride, fasting blood sugar (FBS), and smoking, linear regression analyses were performed separately for SAP and ACS patients. Table 2 shows there was no significant correlations between IL-25 and these risk factors.

## Analyses of coronary artery

### disease risk factors between quartiles of IL-25

Biochemical and demographic characteristics of SAP, ACS, and healthy controls were compared between quartiles of IL-25. In control subjects, triglyceride was significantly lower in the third quartile compared to the second quartile. Other risk factors did not show significant differences.

Analyses of IL-25 serum concentration and the number of vessels with stenosis showed that the mean IL-25 was not significantly different between patients with 1, 2, or 3 vessel disease in either the SAP or the ACS group ( $p \geq 0.05$ ) (data not shown).

## Discussion

Cytokines play an important role in the initiation and perpetuation of atherosclerosis. The possibility that some cytokines, such as IL-25, may be protective against atherosclerosis is currently under investigation. To clarify IL-25's potential role in human CAD disease, we evaluated the association between plasma IL-25 concentrations and the risk of ACS. In contrast to findings regarding the protective role of IL-25 in mouse models of atherosclerosis [4, 18], we found no significant differences

**Table 3. Demography and biochemical characteristics of patients compared in quartiles of serum IL-25 concentrations**

Variables	Study group	Serum IL-25 level				P, value
		Q1 ( $\leq 174$ ng/ml), n=44	Q2 (174–333 ng/ml), n=45	Q3 (333–474 ng/ml), n=45	Q4 ( $> 474$ ng/ml), n=44	
Age (years)	SAP	62.9 $\pm$ 11	62.7 $\pm$ 8.9	58 $\pm$ 7.9	63.2 $\pm$ 12	0.6
	ACS	58.1 $\pm$ 13.7	57.6 $\pm$ 12.4	65.7 $\pm$ 10.1	57.5 $\pm$ 10.6	0.04
	Control	44.8 $\pm$ 7.9	42.6 $\pm$ 10.5	46.5 $\pm$ 11.9	43.5 $\pm$ 9.4	0.8
Gender (%)	SAP	22.2/26.3	11.1/36.8	44.4/10.5	22.2/26.3	0.09
	ACS	19.5/10.6	36.6/44.7	29.3/31.9	14.6/12.8	0.6
	Control	26.7/18.5	40/33.3	20/37	13.3/11.1	0.7
BMI (kg/m <sup>2</sup> )	SAP	25.3 $\pm$ 2.4	23.4 $\pm$ 2.9	23.4 $\pm$ 3.6	25 $\pm$ 4.4	0.5
	ACS	24.5 $\pm$ 4.1	26.2 $\pm$ 4.5	24.5 $\pm$ 4.5	26.9 $\pm$ 3.7	0.2
	Control	26.6 $\pm$ 5.7	25.2 $\pm$ 3.1	24.8 $\pm$ 5.9	24.6 $\pm$ 2.6	0.8
Waist (cm)	SAP	96.1 $\pm$ 6.2	84.5 $\pm$ 13.2	81.7 $\pm$ 13.8	89.8 $\pm$ 12.1	0.06
	ACS	87 $\pm$ 17.2	96.8 $\pm$ 20.1	90.7 $\pm$ 11.2	92.7 $\pm$ 12.9	0.3
	Control	79.2 $\pm$ 21.5	84.7 $\pm$ 10.7	74.6 $\pm$ 18.1	76.4 $\pm$ 10.2	0.4
LDL cholesterol (mg/dl)	SAP	77.7 $\pm$ 22.9	96.2 $\pm$ 38.3	76.3 $\pm$ 23.1	93.2 $\pm$ 34.5	0.5
	ACS	79.1 $\pm$ 16.1	119.8 $\pm$ 77.8	97 $\pm$ 33.5	95.4 $\pm$ 39.2	0.8
	Control	127 $\pm$ 36.9	121.5 $\pm$ 40.3	122.3 $\pm$ 46.3	126.2 $\pm$ 43.2	0.9
HDL cholesterol (mg/dl)	SAP	41.1 $\pm$ 9.5	46.2 $\pm$ 6.7	46 $\pm$ 15.5	44.4 $\pm$ 10.5	0.8
	ACS*	38 (31-52)	37 (31-50)	41 (35-49)	40 (37-43)	0.87
	Control	39.5 $\pm$ 6	42.1 $\pm$ 6.6	40.2 $\pm$ 12.3	45.3 $\pm$ 13.6	0.7
Total cholesterol (mg/dl)	SAP	137.6 $\pm$ 30.9	170.4 $\pm$ 35.2	145.1 $\pm$ 38.6	162.4 $\pm$ 38.4	0.3
	ACS	138.3 $\pm$ 26.2	149.1 $\pm$ 35.9	160.3 $\pm$ 38.3	161.7 $\pm$ 60.1	0.4
	Control	189.5 $\pm$ 36.7	186.8 $\pm$ 41.4	178.4 $\pm$ 44.2	187.7 $\pm$ 45.1	0.9
Triglycerides (mg/dl)	SAP	104.6 $\pm$ 44	114.1 $\pm$ 54.4	121.87 $\pm$ 2.3	146.2 $\pm$ 70.1	0.6
	ACS	104 (83-120)	99 (70-127)	113 (87-129)	142 (85-177)	0.39
	Control	109.7 $\pm$ 35.9	106.2 $\pm$ 36.5	71.2 $\pm$ 25.9	81.3 $\pm$ 40.2	0.03
FBS (mg/dl)	SAP	112.6 $\pm$ 35.1	123.2 $\pm$ 32.6	184.3 $\pm$ 71.3	136.2 $\pm$ 62.3	0.09
	ACS	109.3 $\pm$ 18.4	128 $\pm$ 55.6	150 $\pm$ 82.3	131.7 $\pm$ 49.6	0.3
	Control	91.7 $\pm$ 11.2	92.9 $\pm$ 13.4	96.2 $\pm$ 18.8	103.6 $\pm$ 21.4	0.5
Current Smoker (%)	SAP	25	10	25	40	0.6
	ACS	27.3	40.9	18.2	13.6	0.5
	Control	39	33.3	11	16.7	0.2
Gensini score	SAP	32.5 $\pm$ 42	37.9 $\pm$ 37.5	13.4 $\pm$ 22.4	33.5 $\pm$ 29.5	0.4
	ACS	48 $\pm$ 38.2	65.4 $\pm$ 61.5	68.5 $\pm$ 41.1	54.5 $\pm$ 48.7	0.6

Data are mean $\pm$ SD or median (IQR).



in serum IL-25 concentrations between ACS, SAP patients, and healthy controls, suggesting that this cytokine does not play a protective role in ACS of humans. Furthermore, there were no significant correlations between serum IL-25 concentrations and 1, 2 or 3 vessel disease, as well as between serum IL-25 and clinical characteristics (Table 2).

Mantani et al. demonstrated that IL-25 acts in an anti-atherogenic manner through ILC2 activation. They showed that administration of IL-25 released ILC2s expansion in the spleen, which led to increased levels of B1a cells. These cells secrete athero-protective IgM antibodies, which recognize oxidized LDL and reduce atherosclerosis [4]. The proposed atheroprotective effect of this cytokine is due to the fact that IL-25 is a potent inducer of IL-5, IL-13, and Th<sup>2</sup> related responses [9, 21–24] and is an inhibitor of the Th17 related response [17], both of which are beneficial for atherosclerosis protection [25–28]. Apparently, during hypercholesterolemia, an appropriate concentration of IL-25 can maintain the T-cell subsets, and its absence leads to disturbance of the Th1/Th17 related cytokine balance and increased atherosclerotic plaque formation [18].

However, there is a paucity of literature on IL-25 and human coronary disease. Our results are in accordance with the study of de Boer et al. that investigated the expression of IL-25 in normal and atherosclerotic human arteries and found that these arteries showed strong expression of IL-25 [29]. Interestingly, they found that the strongest IL-25 expression was on mononuclear cells, which were present in the intima and the adventitia of complicated plaques but not in those of normal arteries. However, our results were not consistent with Xu et al.'s study that showed gradually increasing IL-25 concentrations in SAP, UAP, and AMI groups as compared to a control group. Those elevated IL-25 concentrations were positively correlated with the severity of coronary stenoses [30]. The reason for the discrepancy between Xu et al.'s study and the current findings should be further evaluated, since it may reflect the small sample size of both studies.

## Conclusion

Despite the confirmatory evidence in mice and that of the only available human study [30], the current findings did not support positive effect of IL-25 in protecting

ACS disease in humans. It seems that IL-25 does not have potential implications for atherosclerosis development in humans. However, this study is a preliminary report, and our results must be viewed with caution. These data should be confirmed by prospective studies with larger numbers of patients and control subjects.

## Declarations

Ethical approval and consent to participate. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or with comparable ethical standards. Informed consent was obtained from all individual participants included in the study. The ethical committee of the Hormozgan University of Medical Sciences confirmed the study (the committee's reference number: IR.HUMS.REC.1397.008). Consent for publication: not applicable. Availability of data and materials: not applicable.

## Author contribution

NN developed the concept; NN and MR prepared the manuscript; NF performed experimentation; HM and HF performed examinations of patients and angiography; MR analyzed data, prepared tables, and carefully reviewed the manuscript. All authors read and approved the final version of the manuscript.

## Acknowledgment

We extend our thanks to Ms. Gisoo Mehri for helpful comments on our manuscript and the research council of Hormozgan University of Medical Sciences for financial support.

## Funding

This study was supported by research council of Hormozgan University of Medical Sciences (970347).

*No conflict of interest is reported.*

**The article was received on 21/12/2020**

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