

## Original Article

# *Evaluation of Clinical and Laboratory Predisposing Factors of Acute Coronary Syndrome in Military Staff*

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### ABSTRACT

**Background:** Cardiovascular diseases are the leading cause of death in the third millennium. Acute coronary syndrome (ACS) is the most fatal cardiovascular disease, and various factors are involved in the development of this disease. These factors include clinical and laboratory factors as well as stress. Occupational stress is a risk factor for heart disease, and it also increases the risk of coronary heart disease. Military work is universally considered to be stressful. The aim of this study was to evaluate the clinical and laboratory predisposing factors of ACS in military staff.

**Methods:** In this prospective study, 260 patients admitted to Baqiyatallah Hospital were enrolled and divided into 2 groups: 130 patients with ACS and 130 patients with stable coronary artery disease. The study population was studied for various variables, including occupational stress, sedentary lifestyle, and some laboratory markers, including the neutrophil-to-lymphocyte ratio (NLR), the ratio of monocytes to high-density lipoprotein (HDL), and red cell distribution width (RDW).

**Results:** There were significant differences between the 2 groups in terms of physically demanding tasks (case: 61% vs control: 43%;  $P = 0.036$ ), an average daily sitting time of more than 3 hours (case: 58.5% vs control: 43.8%;  $P = 0.048$ ), and an average daily television watching time of more than 2 hours (case: 56.9% vs control: 42.3%;  $P = 0.048$ ). There was a significant difference concerning NLR between the case and control groups (case:  $4.8 \pm 1.4$  vs control:  $2.2 \pm 0.5$ ;  $P = 0.011$ ) regarding the ratio of monocytes to HDL (case:  $16.6 \pm 5.6$  vs control:  $10.6 \pm 3.1$ ;  $P = 0.034$ ) and RDW (case:  $14.5 \pm 1.9$  vs control:  $12.8 \pm 1.4$ ;  $P = 0.041$ ).

**Conclusions:** According to our findings, an increase in NLR and the ratio of monocytes to HDL are predisposing factors of ACS; in addition, RDW is a predicting factor of ACS in military personnel. A sedentary lifestyle and work stress are also contributing factors to the development of ACS in this population. (*Iranian Heart Journal 2021; 22(1): 66-73*)

**KEYWORDS:** Acute coronary syndrome, Plaque rupture, Inflammatory markers

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**A**cute coronary syndrome (ACS) is a clinical event that causes considerable immediate morbidity and mortality and a high risk of a further coronary accident within a year.<sup>1, 2</sup> ACS leads to multiple symptoms such as chest pain, dyspnea, and arrhythmia.<sup>3</sup> Atherosclerotic plaque rupture or erosion is recognized to be the prime triggering factor in ACS, and it is accompanied by local thrombosis activation, which makes this acute incident a potential immediate catastrophe.<sup>3, 5</sup> Atherosclerosis plays a major role in the pathogenesis of life-threatening ACS, including ST-segment elevation myocardial infarction (STEMI), non-STEMI, and unstable angina-the latter, in particular, if acute chest pain occurs at rest.<sup>6, 7</sup> Another common presentation of atherothrombosis is sudden cardiac death.<sup>8, 9</sup> Rare non-atherosclerotic causes of ACS include coronary arteritis, trauma, dissection, thromboembolism, congenital anomalies, cocaine abuse, and complications of cardiac catheterization.<sup>10</sup> A number of intrinsic and extrinsic factors that determine plaque vulnerability have been identified as the size and consistency of the plaque core, the thickness and collagen content of the fibrous cap, and the inflammation within the plaque. Further factors such as hemodynamic stress upon the plaque may ultimately contribute to cap disruption.<sup>11</sup> Endothelial damage allows the passage of inflammatory cells and low-density lipoprotein (LDL) into the vessel intima. Free radicals are responsible for the oxidation of the deposited LDL, and oxidized-LDL promotes cytokine and protease release from macrophages. Proteases (in addition to other factors) degrade the fibrous cap, which causes disruption, allowing the exposure of thrombogenic materials to the provoking component of plasma. In addition, local thrombotic and fibrinolytic activities determine the degree of thrombus progression or dissolution.<sup>11</sup> Military staff members have a critical role in the military society and their

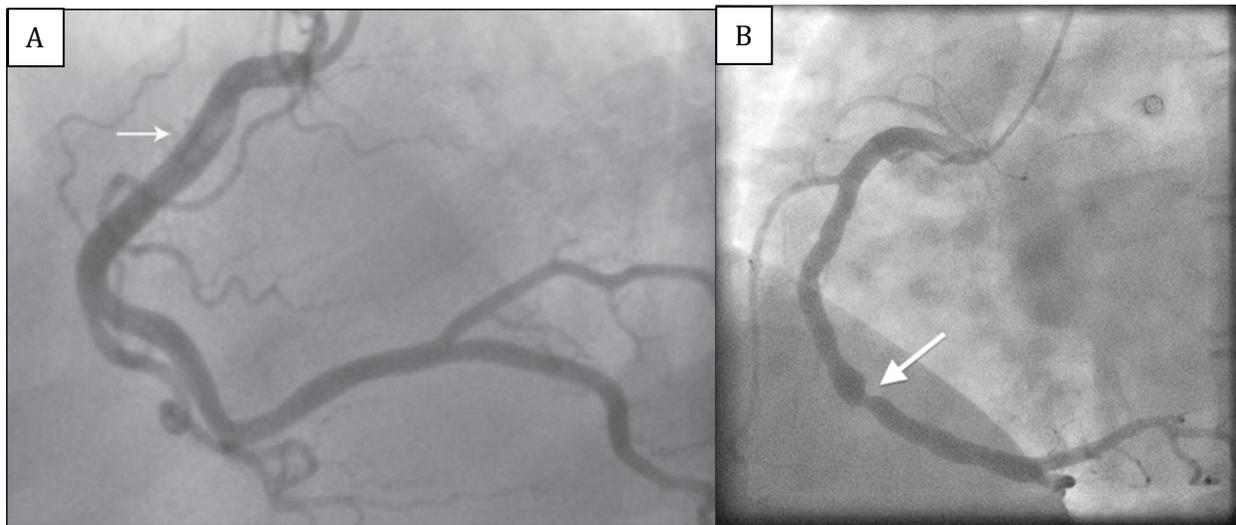
stressful job predisposes them to activation of the atherosclerotic cascade.<sup>12</sup> Based on previous studies, several laboratory factors play an important role in plaque rupture such as neutrophils and monocytes. In this study, we aimed to demonstrate the relationship between these markers and plaque rupture. Additionally, we sought to demonstrate a relationship between daily stress and the burden of cardiovascular problems in military staff.

## METHODS

In this prospective study, 260 patients admitted to Baqiyatallah Hospital were enrolled and divided into 2 groups. The case group was comprised of 130 patients with ACS and probable coronary plaque rupture. These patients had acute STEMI or non-STEMI ACS with positive troponin I and underwent coronary angiography, which showed intracoronary thrombi or irregular lesions with ulceration or flap (Fig. 1A). The control group consisted of 130 patients with stable coronary artery disease (CAD) and without probable plaque rupture. These patients had chronic coronary syndrome and underwent coronary angiography, which showed at least single-vessel disease with a minimum 70% stenosis but without any of the above characteristics of probable plaque rupture in coronary angiography discussed earlier (Fig. 1B).

### Clinical Variables

The clinical variables assessed were age, sex, and known coronary risk factors, which consisted of hypertension (blood pressure  $\geq$  140/90 mm Hg and/or a history of taking antihypertensive medication), diabetes mellitus (fasting plasma glucose  $\geq$  126 mg/dL, plasma glucose  $\geq$  200 mg/dL, or a diabetic pattern on the 75 g oral glucose tolerance test or HgA1C  $>$  6.5 mg/dL in a random blood sample), current smoking, and a family history of CAD in the first-degree relatives.



**Figure 1: A-** Intracoronary thrombus is illustrated at the proximal part of RCA (arrow) in a patient with ACS and positive troponin.

**B-** Significant stenosis is present at the mid-part of RCA (arrow) without any evidence of intracoronary thrombi or ulcerated plaque.

RCA, Right coronary artery; ACS, Acute coronary syndrome

### Blood Sampling and Analysis

Blood samples were collected at baseline in the emergency department. The blood samples were separated by centrifugation, stored at 4°C, and then analyzed (SRL Co, Ltd, Tokyo, Japan). The levels of neutrophils, monocytes, lymphocytes, red cell distribution width (RDW), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured via enzymatic methods.

Work stress was considered to have 2 components: job strain, which combines high work demands and low job control, and effort-reward imbalance, which more closely reflects economic factors in the workplace.

The fact that military staff members play an integral role in any part of the security and safety of a community renders them prone to stress. For the purposes of the present study, we chose military staff members working in an executive capacity because they are exposed to daily job stress and a sedentary

lifestyle coincidentally. We found the following confounding factors as explanations for their predisposition to plaque rupture:

### Demands in the Workplace<sup>12, 13, 24, 25</sup>

1. The amount of work is often so great that there is no time to think of other things.<sup>12, 13, 24, 25</sup>
2. The work needs attention all the time.<sup>12, 13, 24, 25</sup>
3. The work is physically demanding.<sup>12, 13, 24, 25</sup>
4. There are risks for others in the event of mistakes.<sup>12, 13, 24, 25</sup>

### Support in the Workplace<sup>12, 13, 24, 25</sup>

1. There is not always the possibility for advice and help.<sup>12, 13, 24, 25</sup>
2. The employer does not usually offer praise.<sup>12, 13, 24, 25</sup>

**Sedentary Lifestyle**<sup>14, 15, 26, 27</sup>

1. Average daily sitting time of more than 3 hours<sup>14, 15, 26, 27</sup>
2. Average daily television watching time of longer than 2 hours<sup>14, 15, 26, 27</sup>

We also obtained written informed consent from all the patients in this study for participation, medical procedure, and use of clinical information prior to coronary angiography. The study adhered to the rules stipulated by the Medical Ethics Committee of Baqiyatallah Hospital.

**Statistical Analysis**

The variables were presented as mean±SD or counts (percentages). Comparisons between the 2 groups were performed using the Student *t*-test, the Mann–Whitney *U* test, or the  $\chi^2$  test, as appropriate. Age, male sex, coronary risk factors,  $\delta$  LDL-C,  $\delta$  HDL-C, and variables with a *P* value of less than 0.1 in the univariate assessment were entered into a multivariable model. The statistical analyses were conducted using SPSS software, version 22 (IBM Corp). A *P* value of less than 0.05 was considered statistically significant.

**RESULTS**

In this study, 300 patients were enrolled primarily and 40 patients were excluded because of a lack of desired variables. The study population was divided into a case group, comprising patients with the indicators of ACS and probable plaque rupture, and a control group, consisting of patients with stable CAD. In the case group, 64% of the patients were male at a mean age of 58.1 ± 7.4 years and 36% were female at a mean age of 62.7 ± 3.1 years. In the control group, 69% of the subjects were male at a mean age of 56.1 ± 8.5 years and 31% were female at a mean age of 61.4 ± 5.7 years.

**Table 1:** Demographic data

Demographic Data			
Total Number		Case (n = 130)	Control (n = 130)
Age	Male	58.1 ± 7.4	56.1 ± 8.5
	Female	62.7 ± 3.1	61.4 ± 5.7
Gender	Male	83(64%)	89(69%)
	Female	47(36%)	41(31%)

CAD, Coronary artery disease; FFR, Fractional flow reserve; NYHA, New York Heart Association

In the case group, 77% of the patients had single-vessel disease, 13% double-vessel disease, and 10% triple-vessel disease. In this group, 81% of the patients had intracoronary thrombi and 19% had irregular lesions with ulceration or flap. In the control group, 57% of the subjects had single-vessel disease, 27% double-vessel disease, and 16% triple-vessel disease. Patients with characteristics of probable plaque rupture in the control group were excluded from this group.

**Table 2:** Angiographic data

Angiographic Data	Case	Control
Single-vessel disease	77%	57%
Double-vessel disease	13%	27%
Triple-vessel disease	10%	16%
Intracoronary thrombus	81%	
Irregular lesion with ulceration or flap	19%	

There was a significant difference between the 2 groups in 2 components of demands in the workplace: the amount of work is often so great that there is no time to think of other things (case: 68% vs control: 54%; *P* = 0.048) and the work is physically demanding (case: 61% vs control: 43%; *P* = 0.036). The results of the other parameters are shown in Table 3. There was a significant difference between the 2 groups in case of an average daily sitting time of more than 3 hours (case: 58.5% vs control: 43.8%; *P* = 0.048) and the average daily time of television watching of more than 2 hours (case: 56.9% vs control: 42.3%; *P* = 0.048).

**Table 3: Results**

Values	Case%(N)	Control%(N)	P value
<b>Demands in the Workplace</b>			
The amount of work is often so great that there is no time to think of other things.	68% (88)	54% (70)	0.048
The work needs attention all the time.	56% (72)	48% (62)	0.057
The work is physically demanding.	61% (79)	43% (55)	0.036
There are risks for others in the event of mistakes.	66% (85)	58% (75)	0.058
<b>Support in the Workplace</b>			
There is not always the possibility for advice and help.	43% (55)	46% (59)	0.14
The employer does not usually offer praise.	36% (46)	48% (62)	0.21
<b>Sedentary Lifestyle</b>			
Sitting time > 3 h per day	58.5% (76)	43.8% (57)	0.048
Sitting time < 3 h per day	41.5% (54)	56.2% (73)	
Television watching time > 2 h per day	56.9% (74)	42.3% (55)	0.048
Television watching time < 2 h per day	43.1% (56)	57.7% (75)	

There was a significant difference in the HDL-C level between the case and control groups (case:  $44.93 \pm 10.77$  vs control:  $51.02 \pm 8.49$ ;  $P = 0.023$ ), and the HDL-C level in the case group was significantly lower than that in the control group. There was a significant difference in the neutrophil-to-lymphocyte ratio (NLR) between the case and control groups (case:  $4.8 \pm 1.4$  vs control:  $2.2 \pm 0.5$ ;  $P = 0.011$ ). The ratio in the case group was significantly higher than that in the control group ( $P = 0.011$ ). There was a meaningful difference in the ratio of monocytes to HDL between the case and control groups (case:  $16.6 \pm 5.6$  vs control:  $10.6 \pm 3.1$ ;  $P = 0.034$ ), and the level of this ratio in the case group was significantly higher than that in the control group ( $P = 0.034$ ). RDW was also significantly higher in the case group than in the control group (case:  $14.5 \pm 1.9$  vs control:  $12.8 \pm 1.4$ ;  $P = 0.041$ ).

**Table 4: Results**

Values	Case	Control	P value
HDL-C	$44.93 \pm 10.77$	$51.02 \pm 8.49$	0.023
NLR	$4.8 \pm 1.4$	$2.2 \pm 0.5$	0.011
MHR	$16.6 \pm 5.6$	$10.6 \pm 3.1$	0.034
RDW	$14.5 \pm 1.9$	$12.8 \pm 1.4$	0.041

HDL-C, High-density lipoprotein cholesterol; NLR, Neutrophil-to-lymphocyte ratio; MHR, Ratio of monocytes to HDL; RDW, Red cell distribution width

## DISCUSSION

According to recent studies, cardiovascular diseases constitute the most common cause of death in Western countries and Iran. Among the cardiovascular diseases, coronary atherosclerotic disease and specifically ACS have been the utmost devastating conditions with large numbers of physical limitations that diminish patients' quality of life. One of the most important causes of MI is coronary atherosclerotic plaque rupture. Given the necessity to examine the risk factors for coronary atherosclerotic plaque rupture in military populations, we designed the current investigation to evaluate military staff members in an executive capacity, who have many known risk factors such as physical inactivity and daily job stress.

HDL-C and LDL-C, which function to activate the enzymes that are effective in metabolizing lipoproteins, also act as interfaces for lipoprotein binding and cell surface receptors. Low HDL-C levels are a proven risk factor for CAD, and HDL-C potentially has various antiatherogenic properties, including the regulation of reverse transport of cholesterol from arterial wall cells to the liver and steroidogenic organs.<sup>6-19</sup>

In a study by Ozaki et al,<sup>20</sup> the relationship between the presence of thin-cap fibroatheroma, considered to be a vulnerable plaque in pathology, and the HDL-C level was examined. They reported that HDL-C was correlated with the fibrous cap thickness of the culprit lesion in patients with ACS and concluded that HDL-C might be regarded as a therapeutic target for plaque stabilization. In our study, also HDL-C levels were lower in the group with ACS than in the control group.

Hagström et al<sup>21</sup> examined the association between very low levels of HDL-C and the long-term outcomes of patients with ACS. They concluded that very low baseline HDL-C levels had a higher risk of long-term cardiovascular diseases, which is concordant with our finding.

Chen et al<sup>22</sup> reported that lymphocytes were significantly and independently associated with the presence and severity of coronary atherosclerotic disease in the general population. They recommended the use of NLR to predict cardiovascular risk in patients.

Neutrophils are seen as a marker of ongoing inflammation and lymphocytes as a marker of regulatory pathways. NLR, which is calculated via dividing the neutrophil count by the lymphocyte count, is an indication of systemic inflammation and is associated with poor clinical outcomes in various cardiovascular diseases, including ACS. In our study, NLR was significantly different between the 2 groups, and it was higher in the case group. In the study of Chen et al,<sup>22</sup> NLR, as a predictor of myocardial damage and cardiac dysfunction in patients suffering from ACS, was examined and the results showed that NLR was a strong predictor of myocardial damage in patients with acute MI. They reported that a high NLR was associated with myocardial dysfunction in all patients and concluded that severe inflammation (NLR) could predict the

consequence of the heart in patients with ACS.

Increased RDW in patients with ACS is an independent factor and a predictor of inadequate collateral circulation. In our study, the level of RDW in the group with ACS was significantly higher than that in the control group, indicating a significant association between the level of RDW and the risk of ACS. A meta-analysis to study the relationship between RDW and mortality in patients with ACS found that a low RDW level during ACS was associated with lower all-cause or cardiovascular mortality rates and a lower risk of subsequent events.<sup>23</sup>

Bo Netterstrøm et al<sup>24</sup> confirmed the job strain model as well as the well-known association between socioeconomic status and the risk of MI. Peter et al<sup>25</sup> in the SHEEP Study showed an improved risk estimation of acute MI by combining information from the 2 job stress models under study. According to our results, among military staff members with coronary plaque rupture, job strain had a higher incidence, especially in terms of physically demanding tasks in the workplace.

Katzmarzyk et al<sup>26</sup> indicated that life expectancy in the United States would be 2.00 years higher if adults reduced their time spent sitting to below 3 hours per day and 1.38 years higher if they reduced television viewing to below 2 hours per day. In the INTERHEART Study by Claes Held et al,<sup>27</sup> leisure-time physical activity and mild-to-moderate occupational physical activity, but not heavy physical labor, were associated with reduced risk, while ownership of a car and a television set was associated with an increased risk of MI across all economic regions. In our study, we found that among military staff members with plaque rupture, a sedentary lifestyle had a higher incidence, especially in terms of a sitting time of more than 3 hours per day and a television watching time of more than 2 hours per day.

## CONCLUSIONS

According to the results of the present study, an increase in NLR, the ratio of monocytes to HDL, and RDW and a decrease in HDL-C constitute the predisposing factors of ACS. Sedentary lifestyles and job strain are also contributing factors to the development of ACS.

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