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Research Article

# Importance of IL-6 as a Predictor of Disease in Young Military Patients with Arterial Hypertension

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## Abstract

Arterial Hypertension (AH) is one of the most common medical and social problems in the world among able-bodied people. During this period, AH has already expanded its medical scope and acquired a multidisciplinary character, which is of great social importance [1]. In modern times, optimal blood pressure control and its adequate correction significantly reduces the incidence and mortality of diseases of the cardiovascular system, such as stroke, myocardial infarction, heart failure and sudden cardiac death. The development of AH along with atherosclerosis is one of the factors that increase global cardiovascular risk [2]. There is insufficient evidence for both the prevalence and clinical management of hypertension among young servicemen. For this reason, it is necessary to study the clinical effects of high blood pressure levels in young servicemen. Because the direct etiopathogenesis of primary hypertension is very complex and has not been fully studied [15,16].

**Keywords:** Arterial Hypertension (AH); Renin-angiotensin-aldosterone System (RAAS); Endothelium

## Introduction

The pathogenetic link between AH and inflammatory processes is a multicomponent process that includes activation of the sympathetic nervous system, hyperactivity of the renin-angiotensin-aldosterone system (RAAS), and a number of inflammatory processes. An early indicator of the pathogenesis of these combined pathologies is endothelial dysfunction caused by inflammation.

It is known that the vascular endothelium is considered the target organ of AH. It is no coincidence that the vascular endothelium is the largest endocrine gland in the body. Vascular endothelial cells provide the synthesis of a number of biologically active substances involved in the regulation of vascular tone, affecting growth factors, and homeostasis, as well as non-specific inflammatory factors that determine the prognosis of hypertensive vasculopathy [3]. The main role of the endothelium is associated with dilatation of peripheral vessels that provide adequate blood supply to internal organs [4]. The endothelium is also a dynamic system that maintains the normal properties of circulating blood and inhibits leukocyte adhesion by inhibiting hypercoagulability [5]. However, to date, there is no consensus on the initial damage to the vascular endothelium during AH. Thus, while some authors consider endothelial damage as the primary cause, others consider it as a consequence of hypertension.

The role of nonspecific inflammation and cell proliferation in many cardiovascular diseases, as well as in the development of arterial hypertension, has long been discussed by scientists around the world. In addition, non-specific markers of inflammation are one of the main components of hypertensive vascular damage [6]. However, the results of clinical and experimental studies to study the relationship between AH and non-specific inflammatory indicators are numerous and contradictory. According to a number of authors, the development of atherosclerosis, arterial hypertension and chronic heart failure during autoimmune processes is determined not only by classical risk factors, but also by the immune-inflammatory pathogenetic mechanisms of these diseases [7]. Recent clinical studies have shown the role of immune-inflammatory factors in endothelial dysfunction due to pro-inflammatory cytokines and oxidative stress (OS) [8]. Anti-inflammatory cytokines

activate immune processes, inflammatory reactions, endothelial cells, atherosclerosis, coronary heart disease, and the pathogenesis of endothelial dysfunction. Non-specific activation of macrophages and monocytes in severe microcirculatory stress disorders is also considered an inducer of the synthesis of inflammatory cytokines (TNF-α (tumor necrotic factor), IL-6 (interleukin-6), IL-8, etc.) [9].

A number of studies have shown that the levels of cytokines such as IL-6, IL-8, IL-1 and TNF-α in the blood of patients with AH are increased compared to normotensive people [10,11,13]. IL-6 is an anti-inflammatory cytokine that is synthesized by cells of the innate immune system and Th1. Differentiation of B-lymphocytes and activation of T-cells occur under the control of IL-6. The involvement of IL-6 cytokine in target organ damage during AH has been demonstrated. Thus, in laboratory experiments, blockade of the cytokine IL-6 led to a decrease in blood pressure and a decrease in kidney damage [14].

Recently, the attitude of the scientific community to the rejuvenation of cardiovascular diseases has changed significantly [17]. For this reason, our goal was to investigate the relationship between high blood pressure in young hypertensive servicemen and IL-6, a non-specific marker of inflammation.

## Materials and Methods

Our study included 120 servicemen treated at the hospital where we worked from January 2019 to September 2021. Patients were divided into 2 groups. The main group included 55 patients with an AH diagnosis and the control group included 65 practically healthy people without AH.

Prior to data collection, written consent was obtained from each patient and the study was approved by the relevant institutional ethics review committee. AH was diagnosed with systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥ 90 mmHg at rest and a history of hypertensive medication. All patients were evaluated by a panel of nephrologists, cardiologists, endocronologists, and cardiosurgeons. The diagnosis of hypertension was made on the basis of the relevant 2021 clinical protocols of the European Society of Cardiology and the European Society of Hypertension. As our research was conducted mainly on young servicemen, therefore I-II degree hypertensive patients were involved in the process. Patients with hypertension who have a history of hypertension or who have been using antihypertensive drugs for the last 6 months have been identified. Patients with co-morbidities, as well as diabetes mellitus (DD), were not included in the study. Blood samples were taken from patients within 35 days. The laboratory parameters analyzed in this study reflect the average values of 2 measurements performed using the same device at different times. Exception criteria included cranial hemorrhage, systemic inflammatory diseases, cancer, acute coronary syndrome, heart failure, severe valvular disease, renal and hepatic insufficiency, hematological disease, body temperature 37.0°C or higher, presence of active infection, white blood cell (WBC) more than 12,000 cells/μL and the use of anti-inflammatory drugs or antibiotics, etc. includes. The subjects› body weight and height were measured and the body mass index (BMI) was calculated by dividing the body weight by the square of the height ($kg/m^2$).

### Measurement of biochemical parameters

All registered patients underwent a blood test after a 12-hour one-night fast. Laboratory data were obtained from patients' medical records. The following biochemical parameters were recorded: serum glucose, hemoglobin, creatinine, total cholesterol (Total-XS), high-density lipoprotein cholesterol (HDL-XS), low-density lipoprotein cholesterol (LDL-XS), triglycerides (TQ), albumin, hypersensitivity C-reactive protein (hs-CRP) levels, as well as the number of white blood cells, neutrophils and lymphocytes. The neutrophil/lymphocyte ratio-NLR (neutrophil-lymphocyte count ratio) was calculated by dividing the neutrophil count by the lymphocyte count. Renal function was assessed using estimated glomerular filtration rate (e-GFR). E-GFR Dietary Modification in Kidney Disease was calculated using the research equation. The IMMAGE 800 analyzer (Beckman Coulter, CA, USA) was used for nephelometric measurement of serum hs-CRP levels.

### Measurement of IL-6

Blood samples were taken from each patient after a night of fasting at the time of admission. Blood samples were centrifuged at 3000 rpm for 10 minutes, allowing them to clot at room temperature for 30 minutes. Serum samples were separated from the red cell clot as soon as possible after centrifugation to prevent the excretion of IL-6 by the blood cells and to prevent it from incorrectly increasing its values. The separated serum was measured immediately. IL-6 levels were measured at the Central Clinical Laboratory of the General Clinical Hospital of the Armed Forces using IL-6 reagent (chemical luminescence analysis) using the IMMULITE® 1000 system (Siemens Healthcare Diagnostics Inc., United Kingdom) (manufacturer's instructions). The detection or normative limit of the kits was obtained from the manufacturers as follows:

IL-6 (detection limit 0.18-16 pg/mL). The recommended reference range was as follows: IL-6 (0.48 ≤ pg/mL).

### Statistical analysis

Statistical analysis was performed using SPSS for Windows (version 19.0; SPSS Inc., Chicago, IL, USA). Categorical variables are presented as frequency and percentage. The χ2 test and the Fisher precision test were used to compare the categorical variables. The Kolmogorov-Smirnov test was used to estimate the distributions of continuous variables. Continuous variables without normal distribution were analyzed using the Mann-Whitney U-test, and the values obtained were presented as median ($50^{th}$) values and inter-quarter ranges ($25^{th}$ and $75^{th}$). Sensitivity and specificity analyzes were used to draw receiver performance curves. Correlation analyzes were performed using Pearson or Spearman correlation tests. Multivariate logistic regression analysis was used to assess independent risk partners of hypertensive patients. Odds ratios and 95% confidence intervals (CI) were calculated. The probability value of $P < 0.05$ was considered statistically significant.

### The result

A total of 120 servicemen (average age: 36.8 ± 7.7 years) who meet the eligibility criteria were registered for the current study. According to the presence of AH, patients were classified as hypertensive patients (n = 55) and control (n = 65). Table 1 summarizes the initial demographic and clinical characteristics of patients. We did not observe age-related differences in age, SD, smoking status, and history of coronary artery disease (CAD). Hs-CRP (3.09 ± 1.69 mg/dL vs. 1.77 ± 0.84 mg/dL, $p < 0.001$), NLR (2.17 ± 1.34 vs. 1.63 ± 0.57; $p = 0.001$) levels were significantly higher in the hypertensive group than in the control group (Table 1).

In addition, IL-6 levels were significantly higher in the group of young hypertensive servicemen than in the control group (1.12 ± 0.98 ng/mL vs. 1.70 ± 1.25 ng/mL; $p < 0.006$) (Table 1).

Pearseon correlation analysis showed that IL-6 had a direct correlation with hs-CRP and an inverse correlation with NLR (r: 0.36; P = 0.001; r: 0.37; P = 0.001; r: -0.35, respectively. ). The indicators that underlie the one-dimensional variant analysis were subjected to numerous logistic regression analyzes and were important in independently confirming the risk factors associated with hypertension. High serum NLR (OR 1.40; 95% CI 1.15-1.71; p = 0.004) and IL-6 levels (OR 1.81; 95% CI 1.04-2.35; p = 0.052) were identified as independent predictors of symptomatic hypertension (Table 2).

| Parameters | Hypertension (n = 55) | Control (n = 65) | P value |
|---|---|---|---|
| Age, year | 36.58 ± 7.58 | 35.80 ± 8.01 | 0.66 |
| Smoking, n (%) | 38(%69) | 46(%70) | 0.61 |
| Systolic blood pressure (mmHg) | 150.48 ± 9.74 | 110.90 ± 10.27 | <0.001 |
| Diastolic blood pressure (mmHg) | 68.84 ± 9.15 | 69.44 ± 9.45 | 0.07 |
| Body mass index | 23.60 ± 2.57 | 23.40 ± 2.49 | 0.73 |
| Ca-channel blocers | 17 | 0 | <0.001 |
| Beta-blockers | 8 | 0 | <0.001 |
| ACE-inhibitors or ARB | 30 | 0 | <0.001 |
| Hemoglobin, g/dL | 14.88 ± 1.75 | 14.93 ± 1.04 | 0.90 |
| Hemotocrit | 42.09 ± 4.16 | 41.18 ± 2.62 | 0.29 |
| Platelet, $10^3/mm^3$ | 256.50 ± 58.39 | 231.73 ± 53.41 | 0.62 |
| White blood cell number,$10^3/mm^3$ | 8.61 ± 2.53 | 8.18 ± 2.51 | 0.45 |
| Lymphochyte count, $10^3$/mm | 3.92 ± 1.02 | 2.77 + 0.81 | 0.05 |
| Neutrophil count, $10^3$/$mm^3$ | 4.98 + 1.81 | 4.01 + 1.03 | 0.04 |
| NLR $10^3/mm^3$ | 2.17 ± 1.34 | 1.63 ± 0.57 | 0.01 |
| Serum glucose, mg/dL | 100.10 ± 8.86 | 98.83 ± 8.98 | 0.53 |
| Serum creatine, mg/dl | 82.92 ± 14.97 | 80.16 ± 9.46 | 0.36 |
| hs-CRP | 3.09 ±1.69 | 1.77 ± 0.84 | <0.001 |
| IL-6 pg/mL | 1.70 ± 1.25 | 1.12 ± 0.98 | <0.006 |
| e-GFR | 75.50 ± 16.45 | 77.80 ± 16.61 | 0.45 |

**Table 1:** Demographic and clinical indicators of patients.
Note: ACE- Angiotensin-converting Enzyme; ARB- Angiotensin-Receptor Blocker; Ca- Channel Blocker; e-GFR- Glomerular Filtration; BMI- Body Mass Index; NLR- Neutrophil-Lymphocyte Count; İL-6- Interleukin 6.

In the ROC curve analysis, IL-6 levels above 1.36 ng/mL predicted hypertension with 70% sensitivity and 68% specificity (AUC = 0.706, $P < 0.012$) (Figure 1).

## Discussion and Conclusion

In our study, we found that IL-6 values were higher in young hypertensive military patients compared to the normative group. At the same time, another inflammatory marker, hs-CRP, was found to be high in a group of young soldiers with hypertension. In addition to the above, a positive correlation was found between IL-6 and hs-CRP.

| Indicators | OR (95% CI) | P value |
|---|---|---|
| NLR | 1.40 (1.15-1.71) | 0.004 |
| Smoking | 2.161 (0.82-6.01) | 0.341 |
| Age | 0.97 (0.87-1.12) | 0.121 |
| IL-6 pg/mL | 1.81 (1.04-2.35) | 0.052 |
| hs-CRP mg/dL | 0.84 (0.58-1.17) | 0.167 |

**Table 2:** Multivariate logistic regression analysis of independent predictors of hypertension.

**Abbreviation:** CI: Confidence İnterval; NLR: Neutrophil-Lymphocyte Count Ratio; OR: Odds Ratio; Hs-CRP: Highly Sensitive C- Reactive Protein, IL-6: Interleukin-6.

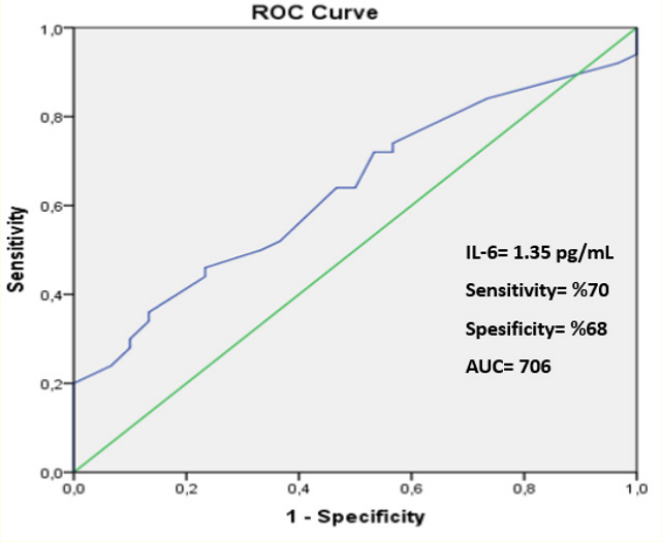


**Figure 2:** Graphical representation of the ROC curve.

Substantial progress has been made in understanding the epidemiology, pathophysiology, and risk associated with hypertension, and a wealth of evidence exists to demonstrate that lowering blood pressure (BP) can substantially reduce premature morbidity and mortality. Despite this, BP control rates remain poor worldwide and are far from satisfactory across Europe. Consequently, hypertension remains the major preventable cause of cardiovascular disease (CVD) and all-cause death globally and in our continent. Reducing SBP to <120 mmHg increased the incidence of CV events and death [26]. For this reason, the early diagnosis of arterial hypertension is very important.

It is a well-known fact that arterial hypertension and hyperlipidemia increase cardiovascular mortality and morbidity [2]. Given that hypertension is the leading cause of death, both in the cardiovascular system and in normal cases, it is clear that the early development of endothelial dysfunction and intravascular inflammatory processes has further increased this ratio. The role of nonspecific inflammation and cell proliferation in many cardiovascular diseases, as well as in the development of arterial hypertension, has long been discussed by scientists around the world [11].

Recent clinical trials have conclusively shown that inflammation is a causative agent in human atherosclerosis. These observations also point to new treatments added to identified treatments to help prevent a growing global epidemic of cardiovascular disease, and also see the use of biomarkers to prescribe anti-inflammatory treatments as a step towards fulfilling the promises of accurate medicine [3].

Non-specific markers of inflammation are one of the main components of hypertensive vascular damage. However, the results of clinical and experimental studies to study the relationship between AH and non-specific inflammatory indicators are numerous and contradictory. According to a number of authors, the development of atherosclerosis, arterial hypertension and chronic heart failure during autoimmune processes is determined not only by classical risk factors, but also by the immunogenic pathogenetic mechanisms of these diseases [12]. Recent clinical studies have shown the role of immunosuppression in endothelial dysfunction due to proinflammation cytokines and oxidative stress [13]. In order to study any connection between the inflammatory process in the body and arterial hypertension, it is first necessary to get acquainted with the origin and causes of inflammation. Inflammation is the body's immune response to any infectious agents that enter it, and involves complex processes such as the activation of inflammatory cells, their migration to damaged tissues, the removal of the infectious agent, and the repair of the damaged area. In addition to inflammatory processes in cardiovascular diseases, the importance of non-specific inflammatory markers (hs-CRP, IL-6, TNF-α, fibrinogen, macrophages, etc.) is often noted [19].

Hs-CRP is an acute phase protein that is involved in many congenital immune reactions and provides phagocytosis and activation of the complement system. Due to the development of Hs-CRP in the future inflammatory process, IL-6, IL-1, IL-8, TNF-α, etc. is

thought to stimulate monocytes to secrete inflammatory cytokines [20,24,25]. For this reason, hs-CRP is considered a marker associated with arterial hypertension. There are many scientific studies that prove the presence of an increase in high-sensitivity hs-CRP in the blood plasma of patients with AH. In addition, hs-CRP values were higher in patients with a tendency to high blood pressure than in normotensive agents [21,26]. Therefore, hypertension is also a low-grade inflammatory condition characterized by the presence of various proinflammation cytokines [22,23]. It is a known fact that the neutrophil/lymphocyte ratio is associated with AH and is a favorable indicator of inflammation that can be easily calculated.

IL-6 is a multifunctional cytokine involved in the regulation of acute phase response and other immune responses, hematopoiesis and chronic inflammatory processes, and is of great importance in the pathogenesis of chronic inflammatory diseases. This cytokine plays an important role in the pathogenesis of atherosclerosis, hypertension, coronary heart disease, chronic heart failure, increases the risk of death from cardiovascular disease and overall mortality. IL-6 is a major pro-inflammatory cytokine responsible for the development of metabolic inflammation, obesity, insulin resistance, and diabetes mellitus.

Therefore, it is expedient to analyze inflammatory cytokines and non-specific inflammatory markers in patients with systemic arterial hypertension, including high concentrations of IL-6.

In our study, we found that IL-6 and hs-CPR were higher in young hypertensive patients than in the normal group. NLR, another indicator of inflammation, was also found to be high in the young hypertensive group. At the same time, there was a positive correlation between IL-6 and hs-CPR, which are considered two inflammatory markers, and a negative correlation between IL-6 and NLR. (r: 0.36; P = 0.001; r: 0.37; P = 0.001; r: -0.35).

As we know, older people, smokers and people with high markers of inflammation have a higher incidence of AH. However, since early detection of arterial hypertension in people who are considered to be relatively young is a very topical issue today, we aimed to obtain results in this direction in our research. According to our results, an increase in IL-6 levels can act as an independent predictor of symptomatic hypertension, regardless of other risk factors that may occur in the future. Thus, according to our results, an IL-6 level greater than ≥1.35 pm/ml determines future hypertension with 70% sensitivity and 68% specificity. Such results provide a basis for the wider and more appropriate use of IL-6 in our daily clinical practice in the future.

## The End

According to our research, serum concentrations of hs-CRP, and IL-6 in young hypertensive young soldiers are higher than in healthy people. We believe that applying such results to our daily practice, especially in young hypertensive patients, in addition to the control of systolic and diastolic blood pressure, the consideration of markers such as IL-6 and hs-CRP can help prevent future cardiovascular events and deaths in such patients.

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