ORIGINAL ARTICLE

UDC: 355/359:61]::616.1-02
DOI: https://doi.org/10.2298/VSP210122030R

# Relationship between plasma high-sensitivity C-reactive protein and traditional cardiovascular risk factors among active-duty military personnel in the Republic of Serbia

## Veza između koncentracije C-reaktivnog proteina visoke osetljivosti u plazmi i tradicionalnih kardiovaskularnih faktora rizika kod aktivnih vojnih lica u Republici Srbiji

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**Abstract**

**Background/Aim.** Approximately one-third of individuals with only one cardiovascular (CV) risk factor or without any, as well as 40% of individuals with a concentration of cholesterol less than average, die from CV diseases (CVD). Recent studies underlined the significant role of inflammation in atherosclerosis and its complications. The aim of this study was to analyze the association of high-sensitivity C-reactive protein (hs-CRP) with traditional risk factors for coronary heart disease. This is the first such study in Serbia. **Methods.** This is an observational cross-sectional study, which included active-duty military personnel of similar socio-epidemiological and economic characteristics. Plasma hs-CRP and traditional CV risk factors were evaluated. The relative CV risk was staged as low (hs-CRP < 1 mg/L), intermediate (hs-CRP between 1 and 3 mg/L), and high (hs-CRP > 3 mg/L). The Systematic Coronary Risk Evaluation (SCORE) system was used for absolute CV risk assessment and total risk (fatal and non-fatal events). **Results.** The study included 205 participants**,** average age of 39 (35–43) years, with median and interquartile range values of hs-CRP 0.80 mg/L (0.43–1.75 mg/L), with average hs-CRP values of 0.71 mg/L in participants younger than 40 years of age and 1.2 mg/L in the older than 40 years. The difference in hs-CRP values between these two groups was statistically significant ($p = 0.006$). There was a significant positive correlation between hs-CRP and age ($r = 0.266$, $p < 0.001$), weight ($r = 0.223$, $p = 0.001$), body mass index (BMI) ($r = 0.344$, $p < 0.001$), diastolic hypertension ($r = 0.190$, $p = 0.007$), LDL cholesterol ($r = 0.152$, $p = 0.032$), triglycerides ($r = 0.144$, $p = 0.039$), number of risk factors ($r = 0.210$, $p < 0.003$), as well as negative correlation with HDL cholesterol concentration ($r = -0.148$, $p < 0.035$). There was no significant correlation between hs-CRP concentration and total cholesterol ($r = 0.131$, $p = 0.062$). According to hs-CRP values, high CVD risk was found in 17.7% of participants older than 40 years of age, and based on SCORE system staging, 90% of participants have intermediate CVD risk. The results of stepwise multiple regression analyses showed that BMI was independently associated with an hs-CRP concentration in the group younger than 40 years of age. Among the older participants, age was found to be associated with concentration of fibrinogen. **Conclusion.** In the population of active military personnel in the Republic of Serbia, hs-CRP is correlated with some of the risk factors for CVD, and only BMI is independently correlated with hs-CRP in those under 40 years of age. Levels of plasma hs-CRP are increased with aging, implying that hs-CRP measurement may provide a more accurate assessment of the individual overall risk profile for CVD in the Serbian military personnel population.

**Key words:**
**cardiovascular disease; high sensitivity c-reactive protein; military personnel; risk factor.**

**Apstrakt**

**Uvod/Cilj.** Skoro trećina osoba bez ili sa jednim faktorom kardiovaskularnog (KV) rizika, kao i 40% osoba sa koncentracijom holesterola manjom od prosečne, umire od KV bolesti (KVB). Nedavna istraživanja su potvrdila značajnu ulogu upale u aterosklerozi i njenim komplikacijama. Cilj rada bio je da se utvrdi povezanost C-

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reaktivnog proteina visoke osetljivosti (hs-CRP) sa tradicionalnim faktorima rizika za koronarnu bolest kod profesionalnih vojnika. Ovo je prvo takvo istraživanje u Srbiji. **Metode.** Studija preseka obuhvatila je aktivna vojna lica sličnih socio-epidemioloških osobina i ekonomskog statusa. Ispitani su hs-CRP u plazmi i tradicionalni faktori KV rizika. Relativni KV rizik definisan je kao nizak (hs-CRP < 1 mg /L), srednji (hs-CRP između 1 i 3 mg/L) i visok (hs-CRP > 3 mg/L). Skala sistemske procene koronarnog rizika (SCORE) je korišćena za procenu apsolutnog i ukupnog KV rizika (fatalni i nefatalni događaji). **Rezultati.** Studija je obuhvatila 205 ispitanika prosečne starosti 39 (35–43) godina, sa srednjom vrednošću i vrednostima interkvartilnog raspona hs-CRP 0,80 mg/L (0,43–1,75 mg/L), sa srednjom vrednošću hs-CRP 0,71 mg/L kod mlađih od 40 godina, odnosno 1,2 mg/L kod starijih od 40 godina. Razlika u vrednosti hs-CRP između ove dve grupe bila je statistički značajna ($p = 0,006$). Zabeležena je značajna pozitivna korelacija između hs-CRP i životnog doba ($r = 0,266$, $p < 0,001$), telesne mase ($r = 0,223$, $p = 0,001$), indeksa telesne mase (ITM) ($r = 0,344$, $p < 0,001$), vrednosti dijastolnog pritiska ($r = 0,190$, $p = 0,007$), LDL holesterola ($r = 0,152$, $p = 0,032$), triglicerida ($r = 0,144$, $p = 0,039$), i broja faktora rizika ($r = 0,210$, $p < 0,003$), kao i negativna korelacija sa koncentracijom HDL holesterola ($r = -0,148$ $p < 0,035$). Nije bilo značajne korelacije između koncentracije hs-CRP i ukupnog holesterola ($r = 0,131$, $p = 0,062$). Prema vrednosti hs-CRP, visok rizik od KVB ustanovljen je kod 17,7% ispitanika starijih od 40 godina, a na osnovu vrednosti SCORE sistema, njih 90% je imalo srednji rizik od razvoja KVB. Rezulati multiple regresione analize pokazali su da je ITM bio nezavisno udružen sa koncentracijom hs-CRP-a u grupi ispitanika mlađih od 40 godina. Kod starijih ispitanika nađena je povezanost godina života i koncentracije fibrinogena. **Zaključak.** U populaciji aktivnih vojnih lica u Republici Srbiji, hs-CRP je u korelaciji sa nekim od faktora rizika od KVB, a samo je BMI u nezavisnoj korelaciji sa hs-CRP i to kod mlađih od 40 godina. Koncentracija hs-CRP u plazmi raste sa starenjem, što ukazuje na to da bi određivanje hs-CRP moglo biti značajno za precizniju procenu profila individualnog rizika od KVB u populaciji vojnog osoblja Srbije.

**Ključne reči:**
**kardiovaskularne bolesti; c-reaktivni protein, visoko osetljiv; kadar, vojni; faktori rizika.**

## Introduction

Recent studies considering innate and acquired immunity pointed out their role in the initiation and progression of atherosclerosis and its complications [1, 2]. Numerous pathophysiological pathways link chronic inflammation, presented as a low-grade systemic inflammatory response (LGI), to the process of atherogenesis and the development of atheroma, unstable plaque, and/or acute coronary syndrome (ACS) [2, 3]. The importance of LGI in the identification of individuals at increased risk for the occurrence of adverse cardiovascular (CV) events has been confirmed in more than 50 prospective epidemiological and clinical studies worldwide [4–6]. These results are very suggestive of the clear link between markers of inflammation and short- and long-term CV outcomes. Inflammation markers (and markers of LGI) also include various acute phase reactants, such as C-reactive protein (CRP) [7].

CRP is produced predominantly in hepatocytes, especially after stimulation with the cytokines IL-6 and IL-1, as a consequence of infection, chronic inflammatory diseases, cancer, and tissue trauma, but the increase of CRP is also related to aging [8, 9]. Serum CRP levels can be determined by both standard and high-sensitivity CRP (hs-CRP) assays in clinical practice. Measurement of hs-CRP levels can accurately detect LGI state [9]. The hs-CRP is also one of the independent parameters to use in a situation where the clinical decision to initiate statin therapy is uncertain. The hs-CRP may also be used in primary prevention as a risk factor for CV disease (CVD) and a well-validated marker for the risk of future atherothrombotic events and CV mortality [6, 10].

As the inflammatory biomarker, hs-CRP adds prognostic information on CV risk comparable to arterial blood pressure (BP) or cholesterol. The prospective cohort studies have supported the view that relatively high levels of hs-CRP in otherwise healthy individuals are linked to an increased risk of sudden cardiac death, future heart attack, stroke, and/or peripheral arterial disease, as well as cardiac events in CVD patients with obesity and complications of diabetes [4, 5, 7, 11]. The values less than 1 mg/L, between 1 mg/L and 3 mg/L, and more than 3 mg/L indicate low, intermediate, or high relative CV risk, respectively [4]. The value of 2 mg/L is often used as CV cut-off in larger clinical studies that dealt with the relationship between inflammation and risk factors (RFs), but it also may be used as a modifier of CV risk and an indicator that may be helpful in the decision about the application of drug therapy [12, 13]. The American College of Cardiology and American Heart Association (ACC/AHA) primary prevention recommendations from 2019 categorize patients at intermediate risk as class IIa, and those with borderline risk as class IIb. They recommend hs-CRP as more predictive in the assessment of CV risk than the traditional CV RFs such as high-density lipoprotein (HDL) or low-density lipoprotein LDL cholesterol [12]. This could be very important if we keep in mind that more than 40% of people with lower-than-average cholesterol values and about one-third of those with no or only one traditional RF die from CVD [14–16].

The Republic of Serbia (RS) belongs to the group of countries with a high risk of developing CVD [17]. RS is a middle-income country, which has undergone significant economic changes and crises in the last 30 years, and, in this context, there are some population groups that have been particularly exposed to a higher risk of developing CVD [18–19]. The recruitment of professional soldiers (PS) should ensure that part of the population that is "healthier" than the general population is being engaged according to the principle of "a

kind of healthy worker effect" or "healthy warrior effect" [20, 21]. The specificity of professional military service due to exposure to stress as preparation for special tasks, i.e., the nature of work, duties, and lifestyle, can further burden the PS in terms of predisposition for the development of CVD [22, 23].

Our study is the first one in RS that has the aim to analyze the association of hs-CRP with traditional RFs for coronary heart disease.

## Methods

This is a prospective cross-sectional study (conducted from September 2018 to July 2019) that included 205 active male military personnel (MP), more than 20 years of age, members of the same military unit, and similar socio-epidemiological and economic characteristics. The study is a part of a scientific project of the Ministry of Defence of the RS named "Primary prevention of ischemic heart disease of professional military personnel and military officers in the Republic of Serbia", which aims to implement modern principles of CVD prevention in the part of the MP that is subject of the regular systematic examinations and, possibly, suggest new ones. That part of the population is, practically, under systemic control, so there is a possibility of daily insight into the health condition of individuals.

According to the current recommendations on the safety and health at the workplace that define periodic examinations of persons at high-risk workplaces, professional members of the Serbian Army under the age of 40 years undergo a regular systematic examination every two years, while those over 40 years have a regular annual systematic examination [24].

Recommendations for primary CVD prevention and systematic assessment of CV risk are applied in men over 40 years and women over 50 years in the postmenopausal period without known CV RFs [17]. Therefore, we divided the MP into two groups, the younger and the older than 40 years.

Anthropometric measurements and calculations included body height and weight as well as body mass index (BMI). The BMI was derived from body weight expressed in kilograms divided by squared body height (kg/m$^2$). Recommended criteria were used for the assessment of overweight and obesity versus normal BMI. Cut-off value for overweight and obesity was BMI $\geq$ 25 kg/m$^2$. By using a flexible inch tape, the waist circumference (WC) was measured at the midpoint between the lower border of the rib cage and the iliac crest. The following cut-off value of the WC was used to assess the abdominal obesity for men: normal < 94 cm, moderate 94–101 cm, and large $\geq$ 102 cm [25].

The systolic BP (SBP) and the diastolic BP (DBP) were assessed by the sphygmomanometer with the participant in a sitting position and recorded as the arithmetic mean of three repeated measurements. All BP measurements were always taken by the same researcher and with the same-sized cuff for adults [17, 26].

According to the classification of the 2018 European Society of Cardiology (ESC) and European Society of Hypertension (ESH) Guidelines, hypertension (HTN) is defined as SBP $\geq$ 140 mmHg and/or the DBP $\geq$ 90 mmHg. All the participants who used antihypertensive therapy over the last 4 weeks were considered to have arterial HTN [26].

Plasma levels of total cholesterol (TC) and LDL-cholesterol, HDL-cholesterol, triglyceride (TG), and hs-CRP were determined by spectrophotometry using the ADVIA 1800 biochemistry analyzer (Siemens Healthcare Diagnostics, Tarrytown, NY, USA). Dyslipidemia is defined as TC > 5.2 mmol/L, TG > 1.7 mmol/L and HDL cholesterol < 1.0 mmol/L, as well as LDL cholesterol $\geq$ 3.4 mmol/L. In individuals with TG levels of 400 mg/dL and more, LDL-cholesterol was assessed by using the Friedewald formula [27].

The hs-CRP values less than 1 mg/L, between 1 mg/L and 3 mg/L, and more than 3 mg/L indicate low, intermediate, or high relative CV, respectively [4]. Smokers were defined as the individuals that have used more than one cigarette a day for at least 1 year or at least 20 packets of cigarettes in their lifetime [27].

The family history of premature CVD is when the occurrence of CVD is in the first generation, before the age of 55 years in men and 65 years in women [17]. The ten-year risk of the first fatal event caused by atherosclerosis, based on clinical features and laboratory tests, was calculated based on the Systematic Coronary Risk Evaluation (SCORE) system [17].

### *Statistical analysis*

Categorical variables, presented as frequencies, were analyzed using the $\chi^2$ test. All continuous variables, presented as mean value (± standard deviation) or median (interquartile range: 25–75 percentile) for normally or non-normally distributed data, were analyzed using the non-parametric Mann-Whitney test and Kruskal-Wallis test. The relationship between variables was tested with Spearman's Rank Order Correlation. The Shapiro-Wilk test was used to test the normality of data distribution. Multiple regression analysis was used for the assessment of each independent variable significance in predicting or influencing hs-CRP (dependent variable). Statistical significance was defined as $p < 0.05$ for all comparisons. All data were analyzed using the Statistical Package IBM-SPSS, version 26.0.

The principles of ICH Good Clinical Practice were strictly followed, and ethical approval No 151/2019 (05/11/2019) from the Ethics Committee of the Military Medical Academy was obtained for the study protocol. Written informed consent was obtained from each participant.

## Results

The basic characteristics of MP are shown in Table 1.

The 10-year risk of the first fatal event caused by atherosclerosis (SCORE risk) was identified in 10% of low-risk subjects (SCORE < 1%), while 90% of subjects were at moderate risk (SCORE $\geq$ 1% and < 5%) (Table 2).

All respondents were divided according to age into two subgroups: those under 40 and those over 40 years of age. In

**Table 1**

**Basic demographic, biochemical, and clinical characteristics of subjects (n = 205)**

| Parameters | Values |
|---|---|
| Demographic | |
| smoking | 61 (29.7) |
| family anamnesis for CVD | 43 (21.0) |
| alcohol | 18 (8.8) |
| body height, cm | 181.00 (177.00–186.00) |
| body weight, kg | 88 (78.75–96.05) |
| waist circumference, cm | 107.00 (100.00–113.50) |
| waist circumference ≥ 102 cm | 144 (70.2) |
| body mass index, kg/m$^2$ | 26.80 (24.80–28.70) |
| Biochemical | |
| cholesterol, mmol/L | 5.30 (4.56–6.13) |
| cholesterol ≥ 5.2 mmol/L | 113 (55.1) |
| triglycerides, mmol/L | 1.17 (0.78–1.74) |
| triglycerides ≥ 1.7 mmol/L | 54 (26.3) |
| HDL cholesterol, mmol/L | 1.26 (1.11–1.50) |
| HDL cholesterol ≥ 3.4 mmol/L | 26 (12.7) |
| glycaemia, mmol/L | 5.40 (5.10–5.80) |
| sedimentation, % | 7.00 (5.00–10.00) |
| creatinine, μmol/L | 81 (74.50–87.00) |
| fibrinogen, g/L | 2.90 (2.40–3.40) |
| hs-CRP, mg/L | 0.80 0.43–1.75) |
| low risk (< 1 mg/L) | 120 (58.5) |
| intermediate risk (1–3 mg/L) | 58 (28.3) |
| high risk ( ≥ 3 mg/L) | 27 (13.2) |
| Clinical | |
| overweight (BMI: ≥ 25 kg/m$^2$) | 149 (72.7) |
| normal (BMI: < 24.9 kg/m$^2$) | 56 (27.3) |
| systolic blood pressure, mmHg | 120 (120–130) |
| diastolic blood pressure, mmHg | 80 (80–80) |

**Values are presented as number (%) or median (interquartile range: 25–75th percentile).**
**CVD − cardiovascular diseases; HDL − high-density lipoprotein; hs-CRP − high-sensitive C-reactive protein; BMI – body mass index.**

**Table 2**

**The Systematic Coronary Risk Evaluation (SCORE) for individuals older than 40 years of age**

| Score (%) | Examinees, n (%) |
|---|---|
| < 1 | 8 (10.1) |
| 1 | 45 (57.0) |
| 2 | 16 (20.2) |
| 3 | 6 (7.6) |
| 4 | 3 (3.8) |
| 5 | 1 (1.3) |

the group of subjects younger than 40, the median age was 36 (34–38) years, while in the group over 40, the median age was 44 (42–47) years ($p < 0.001$) (Table 3).

In the group younger than 40 years, there were significantly lower values of body mass and WC, BP, TC, LDL cholesterol, TG, as well as fibrinogen and hs-CRP (the average value 0.71 mg/L vs. 1.20 mg/L, $p = 0.006$). There were no statistically significant differences between the groups in body height, glycemic value, and HbA1C.

*Distribution of hs-CRP and correlation with risk factors*

The average value of hs-CRP was 0.8 mg/L. Using widely available high-sensitivity assays, hs-CRP levels of < 1 mg/L, 1 mg/L to 3 mg/L, and > 3 mg/ L corresponded to low-, moderate-, and high-risk groups for future CV events; low risk was detected in 58.5% of participants, moderate in 28.3%, and high in 13.2% of participants (Table 1).

**Table 3**

**Biochemical characteristics of participants**

| Parameters | Age of participants (years) | | *p*-value |
|---|---|---|---|
| | < 40 | ≥ 40 | |
| Age, years | 36 (34–38) | 44 (42–47) | < 0.001* |
| Total cholesterol (C), mmol/L | 5.11 (4.37–5.76) | 5.57 (4.94–6.36) | < 0.001* |
| < 5.2 | 65 (51.6) | 27 (34.2) | 0.022** |
| ≥ 5.2 | 61 (48.4) | 52 (65.8) | |
| Triglycerides, mmol/L | 1.08 (0.75–1.43) | 1.40 (0.92–2.17) | 0.005* |
| < 1.7 | 101 (80.8) | 49 (62.0) | 0.005** |
| ≥ 1.7 | 24 (19.2) | 30 (38.0) | |
| HDL-C, mmol/L | 1.25 (1.10–1.46) | 1.32 (1.12–1.56) | 0.198* |
| ≥ 1.0 | 17 (13.5) | 9 (11.4) | 0.823** |
| < 1.0 | 109 (86.5) | 70 (88.6) | |
| LDL-C, mmol/L | 3.21 (2.65–3.94) | 3.45 (3.06–4.23) | 0.030* |
| < 3.4 | 72 (58.5) | 36 (46.2) | 0.116** |
| ≥ 3.4 | 51 (41.5) | 42 (53.8) | |
| Glycemia, mmol/L | 5.40 (5.10–5.80) | 5.50 (5.20–5.90) | 0.154* |
| HbA1c, (%) | 5.50 (5.30–5.60) | 5.75 (5.45–5.97) | 0.138* |
| Fibrinogen, g/L | 2.60 (2.30–3.00) | 3.20 (2.80–3.50) | < 0.001* |
| hs-CRP, mg/L | 0.71 (0.40–1.39) | 1.20 (0.56–2.26) | 0.006* |
| Arterial hypertension | 16 (12.69) | 23 (29.11) | 0.005** |
| Normal arterial tension | 110 (87.3) | 56 (70.9) | |
| Systolic blood pressure, mmHg | 120.00 (120.00–125.00) | 130.00 (120.00–135.00) | < 0.001* |
| Diastolic blood pressure, mmHg | 80.00 (80.00–80.00) | 80.00 (80.00–86.25) | 0.002* |
| Body mass, kg | 87.50 (80.00–96.00) | 91.15 (83.32–97.80) | 0.001* |
| Body height, cm | 181.00 (177.00–186.00) | 181.00 (177.00–185.87) | 0.443* |
| Waist circumference, cm | 105.00 (95.00–112.10) | 110.20 (105.00–116.00) | < 0.001* |
| Body mass index, kg/m$^2$ | 26.40 (24.70–28.60) | 27.41 (25.72–29.77) | < 0.001* |
| normal ( < 24.9 kg/m$^2$) | 41 (32.5) | 15 (19.0) | 0.050** |
| overweight ( ≥ 25 kg/m$^2$) | 85 (67.5) | 64 (81.0) | |

**Values are presented as number (%) or median (interquartile range: 25–75th percentile).**
**HDL – high-density lipoprotein; LDL – low-density lipoprotein; hs-CRP – high-sensitive C-reactive protein.**
*** – Mann-Whitney U test; ** – Chi-squared ($\chi^2$) test.**

In 13% or 10.3% of respondents younger than 40 years, the value of hs-CRP was in the high-risk category, and in those older than 40 years, it was 17.7%. There was a statistically significant difference in the categorization of risk by hs-CRP values in the groups of the younger/older than 40 years (Table 4).

**Table 4**

**Category of relative risk for cardiovascular diseases (CVD) based on high-sensitive C-reactive protein (hs-CRP) levels in participants younger and older than 40 years**

| hs-CRP level (mg/L) | < 40 years | ≥ 40 years | *p*-value |
|---|---|---|---|
| < 1 (low risk) | 83 (65.9) | 37 (46.8) | |
| 1–3 (moderate risk) | 30 (23.8) | 28 (35.4) | 0.025* |
| ≥ 3 (high risk) | 13(10.3) | 14 (17.7) | |

**Values were presented as number (%).**
*** – Chi-squared ($\chi^2$) test**

The significant correlations between some RFs and hs-CRP values were recorded. Those correlations were registered among the hs-CRP values and the age, body weight, BMI, BP and DBP, LDL cholesterol, and TG, respectively. There was a negative correlation between the hs-CRP values and HDL cholesterol, while there was no statistically significant correlation of hs-CRP with the values of TC (Table 5).

**Table 5**

**Correlation of risk factors with high-sensitive C-reactive protein (hs-CRP) values**

| Risk factor | Correlation coefficient* | *p*-value |
|---|---|---|
| Age | 0.266 | < 0.001 |
| Total cholesterol (C) | 0.131 | 0.062 |
| LDL-C | 0.152 | 0.032 |
| HDL-C | -0.148 | 0.035 |
| Triglycerides | 0.144 | 0.039 |
| Arterial hypertension | 0.135 | 0.050 |
| Systolic blood pressure | 0.137 | 0.050 |
| Diastolic blood pressure | 0.190 | 0.007 |
| Body mass | 0.223 | 0.001 |
| Body mass index | 0.344 | < 0.001 |

**HDL – high-density lipoprotein; LDL – low-density lipoprotein.**
*** – Spearman's rank correlation coefficient.**

The correlation between hs-CRP and the number of RF was also statistically significant (r = 0.206, $p$ = 0.003). The value of hs-CRP in subjects without RFs was 0.68 mg/L (0.40–1.15 mg/L), with 1 RFs 0.79 mg/L (0.41–1.54 mg/L),

**Table 6**

**Correlation of the individual number of risk factors with high-sensitive C-reactive protein (hs-CRP) values**

| Individual number of risk factors | Number (%) of participants | hs-CRP, mg/L median (IQR) | *p*-value* | Correlation coefficient** |
|---|---|---|---|---|
| 0 | 54 (26.3) | 0.68 (0.40–1.15) | | |
| 1 | 84 (41.0) | 0.79 (0.41–1.54) | | |
| 2 | 50 (24.4) | 1.16 (0.55–2.92) | 0.037 | r = 0.206, *p* = 0.003 |
| 3 | 16 (7.8) | 1.22 (0.59–2.65) | | |
| 4 | 1 (0.5) | 3.77 (-) | | |

**IQR – interquartile range: 25–75th percentile.**
*** – Kruskal-Wallis test; ** – Spearman's rank correlation coefficient.**

**Table 7**

**Clinical and biochemical characteristics of the subjects according to high-sensitivity C-reactive protein (hs-CRP) value**

| Characteristics | hs-CRP (mg/L) | | *p*-value |
|---|---|---|---|
| | < 3 n = 178 (86.2%) | ≥ 3 n = 27 (13.2%) | |
| Cholesterol, mmol/L | 5.28 (4.51–5.99) | 5.44 (4.63–6.26) | 0.240* |
| Triglycerides, mmol/L | 1.08 (0.78–1.55) | 1.30 (0.97–2.21) | 0.031* |
| HDL cholesterol, mmol/L | 1.29 (1.12–1.54) | 1.16 (1.06–1.37) | 0.008* |
| LDL cholesterol, mmol/L | 3.31 (2.72–3.96) | 3.50 (2.81–4.37) | 0.155* |
| Glycaemia, mmol/L | 5.40 (5.10–5.80) | 5.60 (5.20–6.00) | 0.139* |
| HbA1c, % | 5.50 (5.40–5.60) | 5.80 (5.10-6.30) | 0.633* |
| Fibrinogen, g/L | 2.80 (2.30–3.30) | 3.40 (2.80–3.70) | < 0.001* |
| Systolic blood pressure, mmHg | 120.00 (120.00–130.00) | 120.00 (120.00–130.00) | 0.220* |
| Diastolic blood pressure, mmHg | 80.00 (80.00–80.00) | 80.00 (80.00–85.00) | 0.131* |
| Arterial hypertension ≥ 140/90 mmHg | 28 (15.7) | 11 (25.0) | 0.279** |
| Body mass, kg | 87.00 (78.65–95.20) | 90.50 (80.77–103.35) | 0.077* |
| Body height, cm | 181.00 (176.00–185.00) | 180.00 (173.50–184.50) | 0.449* |
| Waist circumference, cm | 105.00 (95.00–112.10) | 110.20 (105.00–116.00) | < 0.001* |
| <102 | 54 (33.5) | 7 (15.9) | 0.030** |
| ≥102 | 107 (66.5) | 37(84.1) | |
| Body mass index, kg/m$^2$ | 26.50 (24.55–28.34) | 27.63 (26.00–31.10) | 0.004* |
| normal (< 24.9 kg/m$^2$) | 53 (29.8) | 3 (11.1) | 0.043** |
| overweight (≥ 25) kg/m$^2$) | 125 (70.2) | 24 (88.9) | |

**Values were presented as number (%) or median (interquartile range: 25–75th percentile).**
**HDL – high-density lipoprotein; LDL – low-density lipoprotein; HbA1c – glycated hemoglobin.**
*** – Mann-Whitney U test; ** – Chi-squared ($\chi^2$) test.**

**Table 8**

**Univariate and multivariate linear regression analysis of assessment the importance of each independent variable in predicting or influencing high-sensitivity C-reactive protein (hs-CRP) in participants younger and older than 40 years**

| Independent variables | < 40 years | | | | ≥ 40 years | | | |
|---|---|---|---|---|---|---|---|---|
| | univariate analysis | | multivariate analysis | | univariate analysis | | multivariate analysis | |
| | Beta | *p*-value | Beta | *p*-value | Beta | *p*-value | Beta | *p*-value |
| Age | 0.143 | 0.110 | 0.050 | 0.602 | 0.264 | 0.019 | 0.190 | 0.030 |
| Cholesterol (C) | 0.081 | 0.367 | | | -0.041 | 0.717 | | |
| Triglycerides | 0.019 | 0.832 | | | 0.198 | 0.080 | | |
| HDL-C | -0.094 | 0.298 | -0.075 | 0.414 | -0.240 | 0.033 | -0.169 | 0.145 |
| LDL-C | 0.127 | 0.161 | | | -0.044 | 0.705 | | |
| Fibrinogen | 0.216 | 0.021 | 0.183 | 0.057 | 0.069 | 0.561 | 0.269 | 0.026 |
| BMI | 0.274 | 0.002 | 0.240 | 0.012 | 0.132 | 0.248 | -0.093 | 0.453 |
| Systolic BP | 0.035 | 0.698 | | | 0.086 | 0.453 | | |
| Diastolic BP | 0.055 | 0.547 | | | 0.145 | 0.206 | | |
| AH | -0.032 | 0.722 | -0.065 | 0.485 | 0.225 | 0.048 | 0.199 | 0.093 |

**HDL − high-density lipoprotein; LDL − low-density lipoprotein; BMI − body mass index; BP – blood pressure; AH – arterial hypertension.**
**hs-CRP is a dependent variable (Multivariate analysis in the group < 40 years: F = 2.917, *p* = 0.017, $R^2$ – R-squared 12.0%; Multivariate analysis in the group ≥ 40 years: F = 3.678, *p* = 0.005, R-squared 21.8%).**

with 2 RFs 1.16 mg/L (0.55–2.92 mg/L), and in subjects with 3 RFs was 1.22 mg/L (0.59–2.65 mg/L) (Table 6).

Our results single out a group of 27 (13%) subjects with hs-CRP values > 3 mg/L (Table 7). In this group, compared to group with hs-CRP values 3 mg/L and less, TG, fibrinogen, WC and BMI values were significantly higher, but the HDL cholesterol concentration was lower ($p = 0.031$, $p < 0.001$, $p < 0.001$, $p = 0.004$, $p = 0.008$, respectively).

Multiple regression analysis pointed out that age and fibrinogen had a significant effect on hs-CRP in the group of individuals older than 40 ($p = 0.030$ and $p = 0.026$, respectively). Among the younger, only BMI had an effect on hs-CRP ($p = 0.012$) (Table 8).

## Discussion

This is the first study in Serbia to investigate the association of hs-CRP with RF in a healthy male population. The results of our study showed that hs-CRP as a measure of LGI identifies 27 (13%; 13 younger than 40 years, 14 older than 40 years) subjects with a high relative risk for coronary occlusive disease, in contrast to the SCORE system that identified only intermediate risk subjects. The hs-CRP values correlate with individual RFs (age, BMI, body weight, TG values, negative correlation with HDL cholesterol values) but not with TC values. The correlation is the most significant between age and BMI. Moreover, the research showed that hs-CRP is significantly correlated with the number of RFs of individual participants. Furthermore, stepwise multiple regression analysis points out that age and fibrinogen significantly affect the value of hs-CRP in the participants older than 40 years and BMI in the younger group.

According to the European Association of Cardiologists and a European study that involved 7 countries, there are growing trends in mortality in RS, which is part of the phenomenon observed in Eastern European countries during the second half of the last century [18]. It is also stated that reliable and complete official data on mortality are not available for RS due to war events and reforms, which prevented the systematic collection of data [18].

The average value of hs-CRP among our study participants was 0.8 mg/L. Data on hs-CRP values in “apparently healthy” in RS are unavailable to us. In healthy young adults (both sexes, age 18–63 years) volunteer blood donors, the median concentration of hs-CRP is 0.8–10 mg/L (90th – 99th percentile) [8]. In the United States, 56% of the male population has hs-CRP values up to 1.9 mg/L. The age group of 30–49 years (51% of all) of both sexes has the same value [28]. The HUNT study [29] pointed out that the average value of hs-CRP in the male aged 49.7 ± 16.2 is 1.0 mg/L (IQR 1.8 mg/L), which is comparable to our results, with the notice that the average age in our group is significantly lower, i.e., 39 (35–43) years. It is well known that hs-CRP values “increase” with age, and in this context, the hs-CRP values of our group are equivalent to the significantly older population Norwegian study population [30, 31]. In a study population of 507 healthy people of different ages, the CRP value in individuals under the age of 40 years was 0.95 (± 0.37) mg/L, and in the age between 40 and 44 years was 1.17 (± 0.59) mg/L [32]. In Chinese middle-aged males, the value of hs-CRP is 1.24 (0.65–2.57) mg/L [33].

It should be emphasized that the values of hs-CRP are different in the Asian and European populations, so they are variable depending on the ethnic origin [34, 35]. In the Whitehall II study, a long-term prospective cohort of 7,636 British civil servants with an average age of 50.7 ± 6.6 years, hs-CRP values are 0.84 mg/L (IQR, 1.30 mg/L), and according to this and the previously cited Norwegian study, our study group hs-CRP values are comparable to the values for the elderly persons [36]. An explanation for these values in our group may be the fact that almost 73% of our participants are overweight with BMI ≥ 25 kg/m$^2$, which strictly correlates with hs-CRP values. Adipose tissue has a great inflammatory potential, especially the central type of obesity recorded in 70% of our study participants, also in one-third of respondents with at least 2 RFs, affecting LGL [4, 6, 37, 38].

According to ESC recommendations, SCORE risk is calculated in individuals over 40 years of age. According to the SCORE risk, 90% of respondents belong to the group of medium (moderate risk), and 10% are low risk (Table 2). The lifestyle change is the therapy of choice in those patients. In case of inefficiency of this strategy, in low-risk persons, it is recommended to consider the use of drugs in individuals with LDL cholesterol values of 3.0–4.9 mmol/L, and the use of drugs is recommended when LDL cholesterol values are > 4.9 mmol/L; in case of SCORE risk 1–5% (moderate risk) with LDL cholesterol values of 2.6–4.9 mmol/L, the use of drugs may be considered, and in case of LDL cholesterol values over 4.9 mmol/L, drug therapy should be considered [39]. We did not have subjects with LDL cholesterol values > 4.9 mmol/L.

According to the Centers for Disease Control and Prevention and the American Heart Association criteria, hs-CRP values > 3 mg/L are qualified as "high risk", and, therefore, 27 (13.2%) individuals in our study are at “high risk", which would imply the use of drug therapy [4, 13]. That also means that 14 (17.7%) participants older than 40 years should have drug therapy. Particularly important is the fact that 13 (10.3%) respondents under the age of 40 (the group that is not included in the recommendations of primary prevention based on SCORE) should have drug therapy [17].

We wittingly did not use the Reynolds Risk Score for men to have a comparison of only two scores for total CV risk, which are based on different models [40].

Our research showed that hs-CRP positively correlates with some RFs, especially with age, body weight, BMI, DBP values, LDL cholesterol, and TG values, and has negative correlation with HDL cholesterol values (Table 5). The correlation between hs-CRP and traditional RFs has already been proven, but the relationships are not completely clear [4, 6, 41, 42]. Inflammation is present in all stages of atherosclerosis, and it is the basic

pathophysiological process of CVD [1, 2]. On the other side, according to generally accepted views, the risk of developing CVD depends on the influence and number of traditional RFs [13, 17, 40]. The complexity of the pathophysiological process in inflammation and its links with RFs was underlined in well-documented studies (JUPITER and CANTOS) [43, 44]. Those studies referred to CV mortality decrement as the result of inflammation reduction [43, 44]. It seems to be very important to have in mind that 40% of people with lower-than-average cholesterol values and about one-third of those with no or one traditional RF die from CVD [13–15].

The results of the JUPITER, and later the CANTOS study, could shift principles and focuses on primary and secondary prevention of CVD. The JUPITER study with prospective follow-up showed that statin therapy improved CV outcomes in individuals with hs-CRP values > 2 mg/L and LDL cholesterol values < 3.4 mmol/L without a previous history of coronary heart disease [43]. The CANTOS study practically confirmed the inflammatory hypothesis in the development of atherosclerosis [44]. The CANTOS study showed that reducing inflammation by inhibiting IL-1β significantly reduced vascular risk beyond the level that can be achieved by lowering lipid concentrations. CANTOS further showed a 31% reduction in CV mortality and all-cause mortality among canakinumab-treated patients who achieved the greatest reduction in hs-CRP, as well as therapy efficacy in high-risk patients with chronic kidney disease and diabetes [44]. Such results impose a special role of LGI inflammation in the prevention of CVD.

Both ESC recommendations in the treatment of dyslipidemias as well as ESC recommendations for primary prevention neglect the importance of hs-CRP, while ACC/AHA recommendations are significantly more liberal in this context. Bearing in mind that MPs belong to a particularly "sensitive category" due to the specificity of the workplace, any data that would indicate an increase in both relative and absolute risk among this population is more than welcome. In this context, our results single out a group of 27 (13%) subjects with hs-CRP values > 3 mg/L. These are subjects with an increased inflammatory response expressed through hs-CRP that should not only be linked with CVD but may also be used in the prediction of certain malignant diseases [8, 9].

The incidence of premature CVD has not decreased, while the prevalence of obesity, arterial HTN, and diabetes increased in the younger population, which poses a specific and growing therapeutic challenge [45]. Furthermore, the results of the INTERHEART study (Effect of Potentially Modifiable Risk Factors Associated with Myocardial Infarction in 52 Countries) showed that 9 traditional RFs pose 90% of the population's risk for myocardial infarction, particularly influencing young people that are less aware of their RFs, and would, therefore, participate less in primary prevention programs [46, 47].

A particular problem is the identification of the total CV risk in the part of the population younger than 40 years, for which there is no validated and generally accepted algorithm, except recently published individual standardizations adapted to particular regions [48]. There are over 250 similar logarithms, and another CV calculator probably will not be needed [49]. However, MPs belong to the specific part of the population, which are, according to their professional obligations, to a great degree exposed to the risk of developing CVD [22, 23]. They are mostly younger than 50 years, and it is of primary significance that prevention of CVD and preclinical atherosclerosis in this population be implemented into their regular systematic examinations [45, 50].

Last but not least, multiple regression analysis showed that age and fibrinogen have a significant influence on the increase in hs-CRP values in the group older than 40 years, while in younger people, only BMI has such influence on hs-CRP. These results are in accordance with recently published study data considering the relationship between inflammation and aging [30, 31, 33]. Interestingly, age has no significant influence on hs-CRP in younger people. This is due to the fact that the older group has been exposed to RFs for a long time, as well as that the number of RFs increases with age [30, 42, 48].

Taking these facts into account and incorporating them into the context of professional military service, we tried to adapt this knowledge to our circumstances in order to early detect high-risk individuals for the development of CVD followed by adequate primary prevention measures implementation.

Based on the previously presented facts, it may be advised, in addition to ESC recommendation standards for primary prevention, to evaluate hs-CRP as an affordable biomarker that might help identify individuals who should be under more frequent medical supervision. It provides reliable information for early clinical diagnosis and treatment of incident CVD, as well as monitoring the therapeutic effect of the anti-inflammatory therapy.

### *Limitations of the study*

Bearing in mind that recommendations for primary CVD prevention and systematic assessment of CV risk are applied in men over the age of 40, we divided the MP into two groups – younger and the older than 40 years of age – who are members of the same military unit, with similar socio-epidemiological and economic characteristics. Our study is the first one in RS with the aim to analyze the association of hs-CRP with traditional RFs for coronary heart disease but has some limitations considering study population size and diversity (no females) that may influence the generalization of the obtained conclusions.

## Conclusion

In the population of active military personnel in the RS, hs-CRP is correlated with some of the risk factors for CVD, but only BMI is independently correlated with hs-CRP in those under 40 years of age. Levels of plasma hs-CRP are increased with aging, implying that hs-CRP

measurement may provide a more accurate assessment of the individual overall risk profile for CVD in the Serbian MP population.

**Conflict of interest**

Not applicable.

**Acknowledgements**

We are grateful for the assistance of the Ministry of Defence of the Republic of Serbia, which authorized the project – Primary prevention of ischemic heart disease among active military personnel and civilian personnel in the military in the Republic of Serbia (MFVMA/5/17-19).

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Received on January 22, 2021
Revised on March 18, 2021
Accepted on March 19, 2021
Online First March 2021