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*VEZA IZMEDJU KONCENTRACIJE PLAZMA HS CRP-A I TRADICIONALNIH KARDIOVASKULARNIH FAKTORA RIZIKA U AVL U REPUBLICI SRBIJI*

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VEZA IZMEDJU KONCENTRACIJE PLAZMA HS CRP-A I TRADICIONALNIH KARDIOVASKULARNIH FAKTORA RIZIKA U AVL U REPUBLICI SRBIJI

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running title: high-sensitivity C-reactive protein and traditional cardiovascular risk factors among active duty military personnel in Republic of Serbia
Abstract

**Background/Aim.** Approximately one third of individuals with no or one risk factor, as well as 40% individuals with concentration of cholesterol less than average die from cardiovascular disease (CVD). Recent study underlined significant role of inflammation in atherosclerosis and its complications. Our study is the first one in Serbia which have for the aim that analyses the association of high-sensitivity C-reactive protein (hs-CRP) with traditional risk factors for coronary heart disease.

**Methods:** This study is observational cross-sectional study which included 205 active-duty military personnel similar socioepidemiological and economic characteristics. Plasma high-sensitivity C-reactive protein (hs-CRP) and traditional cardiovascular risk factors were evaluated. The relative cardiovascular risk was staged as low (hs-CRP <1mg/L), intermediate (hs-CRP between 1 and 3mg/L) and high (hs-CRP >3mg/L). The Systematic CORonary Risk Evaluation (SCORE) system was used for absolute cardiovascular risk assessment, and total risk (fatal and non-fatal events).

**Results:** Our 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), with average hs-CRP values 0.71mg/L in the younger than 40 years and 1.2 mg/L in the older. Between the study groups the significant derference in hsCRP-a values was registered; hs-CRP was significantly higher in the group older than 40 years (p=0.006). There was a significant positive correlation between hsCRP 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=-0.159, p<0.023). There was no significant correlation between hsCRP concentration and total cholesterol (r=0.131, p=0.062). According to hs-CRP values, high CV risk was found in 17.7% participants older than 40 years, and based on SCORE system staging, 90% participants have intermediate CV risk. The results of stepwise multiple regression analyses showed that BMI was independently associated with hsCRP concentration in the group younger than 40 years. Among the older, age was found to be associated with fibrinogen values.

**Conclusions.** 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 serum hs-CRP are increased with aging, imply
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:
high-sensitivity C-reactive protein, traditional cardiovascular risk factors.

Apstrakt

Uvod / Cilj. Skoro trećina osoba bez ili s jednim kardiovaskularnim faktorom rizika, kao i 40% osoba s koncentracijom holesterola manjom od prosečne, umire od kardiovaskularnih bolesti (KVB). Nedavno istraživanje je podvuklo značajnu ulogu upale u aterosklerozi i njenim komplikacijama. Naše istraživanje je prvo u Srbiji koje ima za cilj analizu povezanosti C-reaktivnog proteina visoke osetljivosti (hs-CRP) s tradicionalnim faktorima rizika za koronarnu bolest srca kod profesionalnih vojnika. Metode. Studija preseka je obuhvatila 205 aktivnih vojnih lica. Najznačajnije praćene varijable su visokosenzitivni C-reaktivni protein (hs-CRP) i tradicionalni faktori kardiovaskularnog rizika. Relativni kardiovaskularni rizik definisan je kao nizak (hs-CRP <1mg /L), srednji (hs-CRP između 1 i 3mg /L) i visok (hs-CRP> 3mg/L). Apsolutni kardiovaskularni rizik procijenjen je prema skali sistemaske procene koronarnog rizika (SCORE). Rezultati. Studija je obuhvatila 205 pacijenata sličnih socioepidemioloških i ekonomskih karakteristika, prosečne starosti 39 (35-43) godina, sa srednjim i interkvartilnim vrednostima raspona hs-CRP 0.80 mg/L (0.43-1.75), sa srednjom vrednošću hsCRP 0.71mg/L kod mlađih od 40 godina, te 1.2 mg/L kod starijih. Izmedju grupa je nadjena razlika u pogledu vrednosti hs-CRP-a, koje je bio značajno viši u grupi starijih od 40 godina( p=0.006). Zabeležena je značajna pozitivna korelacija između hsCRP i životne dobi (r = 0.266, p <0.001); ), telesne težine (r = 0.223 p = 0,001), indeksa telesne mase (BMI) (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 s koncentracijom HDL holesterola (r = -0.148 p <0,035). Nije bilo značajne korelacije između koncentracije hsCRP i ukupnog holesterola (r = 0.131, p = 0.062). Prema vrednosti hs-CRP, visok rizik od KVB pronaden je u 17,7% ispitanika starijih od 40 godina, a na osnovu vrednosti SCORE sistema, 90% ispitanika u grupi starijih od 40 godina života ima
srednji rizik od KVB. Rezultati multiple regresione analize su pokazali da je BMI bio nezavisno udržen sa koncentracijom hsCRP-a u grupi mladih od 40 godina, a dok je kod starijih od 40 godina nadjena povezanost godina i koncentracija fibrinogena sa vrednošću hs-CRP-a. **Zaključak.** U populaciji aktivnih vojnih lica u Republici Srbiji, hs-CRP je u korelaciji s nekim od faktora rizika za KVB, a samo je BMI u nezavisnoj korelaciji sa hs-CRP i to kod mladih od 40 godina. Koncentracija hs-CRP raste sa starenjem, što govori u prilog značaja određivanja hs-CRP u preciznoj proceni pojedinačnog ukupnog profila rizika za KVB u populaciji vojnog osoblja Srbije.

**Ključne reči:** C-reaktivni protein visoke osetljivosti, tradicionalni kardiovaskularni 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), 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 events has been confirmed in more than 50 prospective epidemiological and clinical studies worldwide (4-6). These results are very suggestive for the clear link between markers of inflammation and short- and long-term cardiovascular outcomes. Inflammation markers (and and markers of LGI) also include various acute phase reactants, 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, tissue trauma, but the increase CRP is also related to the 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 low-grade inflammatory state (9). The hs-CRP is also one of the independent factors to use in a situation where the clinical decision to initiate statin therapy is uncertain (13). The hs-CRP may also be used in primary prevention as a risk factor for cardiovascular disease (CVD),
and a well-validated marker for the risk of future atherothrombotic events and cardiovascular mortality (6, 10).

As the inflammatory biomarker, hs-CRP adds prognostic information on cardiovascular (CV) risk comparable to arterial blood pressure or cholesterol. The prospective cohort studies have supported 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, between 1 and 3, and more than 3 mg/L indicate low, intermediate or high relative cardiovascular risk, respectively (4). The value 2 mg/l is often used as cut off in larger clinical studies that were dealt with the relationship between inflammation and risk factors, but it also may be used as a modifier of CV risk and an indicator that may be helpful in the decision in the application of drug therapy (12-13). The American College of Cardiology and American Heart Association (ACC/AHA) primary prevention recommendations from 2019 categorize the measurement of in class IIa for patients at intermediate risk, and IIb in those with borderline risk. They recommend hs-CRP as a more predictive in the assessment of CV risk than the traditional CV risk factors such as HDL or LDL cholesterol (12). This seems to be very important having in mind that more than 40% of people with lower-than-average cholesterol values, and about one third of those with no or one traditional risk factor die from CVD (14-16).

The Republic of Serbia (RS) belongs to the group of countries with high risk for the development of 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 a part of the population that is "healthier" than the general population, 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 a preparation for special tasks, i.e., the nature of work, duties, lifestyle, can further burden the PS in terms of predisposition for the development of CVD (22-23).

Our study is the first one in Serbia that have the aim to analyse the association of hs-CRP with traditional risk factors for coronary heart disease.
Methods
This is a prospective cross-sectional study (from September, 2018 to July, 2019) that included 205 active military personnel (MP), males, more than 20 years old, members of the same military unit, similar socioepidemiological and economic characteristics. The study is part of the scientific project of the Ministry of Defense of the Republic of Serbia named "Primary prevention of ischemic heart disease of professional military personnel and military officers in the Republic of Serbia", which aim is to implement modern principles of CVD prevention in the part of the military population 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 the possibility of daily insight into the health condition of individuals.

According to the current recommendations on the safety and health at the workplaces, that define periodic examinations of persons at high-risk workplaces, professional members of the Serbian Army under the age of 40 years are undergone to the regular systematic examination every other year, while persons 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 in women over 50 years in the postmenopausal period, without known CV risk factors (17). Therefore, we divided the MP into two groups of the youngers and the olders 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. Cutoff value for overweight and obesity was BMI ≥ 25kg/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 ≥102 cm (25).

The systolic and the diastolic blood pressure (SBP and DBP) were assessed by the sphygmomanometer with 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 2018 European Society of Cardiology (ESC) and European Society of Hypertension (ESH) Guidelines hypertension (HTN) is defined as office systolic blood pressure ≥140 mmHg and/or the diastolic blood pressure ≥90 mmHg. The persons with arterial hypertension were all the participants who used antihypertensive therapy over the last 4 weeks (26).

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

The hs-CRP values less than 1, between 1 and 3, and more than 3 mg/L indicate low, intermediate or high relative cardiovascular risk, 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-square 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 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 on 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.
Ethics of the study: 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.

Results

Characteristics of the participants

The basic characteristics of MP are shown in Table 1. The group of 205 MP males with an average age of 39 years; the majority patients (70%) are non-smokers, and 21% of participants have a family history of premature CVD. More than half of the respondents have values of total cholesterol higher than tolerable, almost 46% have LDL values higher than normal, and about 26% of respondents have elevated triglyceride values. About 70% of the respondents have a waist circumference higher than optimal, and almost 73% of the participants have the increased BMI. 39 subjects or 19% have arterial hypertension.

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

All respondents were divided according to age into two subgroups, those who were under 40 and those who were over 40 years old. In the group of subjects younger than 40 years, the median age was 36 (34-38), while in the group over 40 it was 44 (42-47) years (p <0.001) (Table 3).

In the group younger than 40 years, there are significantly lower values of body weight and waist circumference, blood pressure, total cholesterol, LDL cholesterol, triglycerides, as well as fibrinogen and hs-CRP (the average value 0.71mg/L vs 1.20mg/L, p=0.006). There are no statistically significant differences between the groups in body height, glycemic value and HbA1C.

Distribution of hsCRP and correlation with risk factors

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

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

The significant correlations between some risk factors (RFs) and hs-CRP values were recorded. Those correlations were registered among the hs-CRP values and the age, body weight, BMI, blood pressure and diastolic blood pressure, LDL cholesterol, and triglycerides respectively. There is a negative correlation between the hs-CRP the values and HDL cholesterol, while there is no statistically significant correlation hs-CRP with the values of total cholesterol (Table 5).

The correlation between hs-CRP and the number of RF is also statistically significant (r = 0.206, p = 0.003). The value of hs-CRP in subjects without RF is 0.68 mg/L (0.40-1.15), with 1 RF 0.79mg/L (0.41-1.54), with 2 RF 1.16 mg/L (0.55-2.92), and in subjects with 3 RFs is 1.22 mg/L (0.59-2.65) (Table 6).

Our results single out a group of 27 (13%) subjects with hs-CRP values >3mg/L (Table 7). In this group, comparing to group with hs-CRP values 3mg/L and less, triglycerides, fibrinogen, waist circumference 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).

Multiple regression analysis points out that age and fibrinogen have the significant effect on hs-CRP in the group of individuals older than 40 (p=0.030, p= 0.026). Among the youngers only BMI has the effect on hs-CRP (p=0.012) (Table 8).

Discussion

This is the first study in Serbia examine the association of hs-CRP with risk factors in a healthy male population. The results of our study showed that hs-CRP as a measure of LGI identifies 27 (13%; 13 youngers 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, triglyceride values, negative correlation with HDL values), but not with total cholesterol values. The correlation is the most significant with age and BMI. Also, the
research showed that hs-CRP is significantly correlated with the individual number of risk factors of the participant. Furthermore, stepwise multiple regression analysis points out years and fibrinogen significantly affect the value of hs-CRP in the group older than 40 years, and BMI in the younger group.

According to the European Association of Cardiologists, and in the European study of 7 countries, there are growing trends in mortality in Serbia, which is part of the phenomenon that was 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 Serbia, due to war events and reforms, which prevented the systematic collection of data (18).

The average value of hs-CRP among our study participants is 0.8 mg/L. Data on hs-CRP values in “apparently healthy” in Serbia are not available 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 same value has the age group of 30-49 years (51% of all) of both sexes (28). The HUNT study pointed out that the average value of hs-CRP in the male population aged 49.7±16.2 is 1.0 mg/L (IQR 1.8), which is comparable to our results, with the notice that the average age in our group is significantly lower, ie. 39 (35-43) years (29). 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). 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 0.84mg/L (IQR, 1.30), and according to this and the previous 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 ≥25kg/m2 that strictly correlates with hs-CRP values. Adipose tissue has a great inflammatory potential,
especially the central type of obesity recording in 70% of our study participants, also with a one third of respondents with at least 2 RFs, affecting LGL (4, 6, 37-38).

According to ESC recommendations, SCORE risk is calculated in the persons 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 3.0-4.9 mmol/L, and 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 values over 4.9 mmol/l drug therapy should be considered (39). We did not have subjects with LDL values >4.9 mmol/L.

According to the Centers for Disease Control and Prevention and the American Heart Association criteria, hs-CRP values >3mg/L is qualified as "high risk", and therefore 27 individuals (13.2%) of our study subjects are in “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. Particulary 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 consciously 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, diastolic blood pressure values, LDL and triglyceride values, with negative correlation with HDL values (Table 5). The correlation between hs-CRP and traditional RFs has been already 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 processes in inflammation and its links with RFs was underlined in well-documented studies (JUPITER and CANTOS) (43,44). Those studies referred cardiovascular mortality decrement as the result of inflammation reduction (43,44). It seems to be very important having 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 in primary and secondary prevention CVD. The JUPITER study with prospective follow up showed that statin therapy improved cardiovascular outcomes in individuals with hs-CRP values >2 mg/L and LDL 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-1b significantly reduced vascular risk, beyond the level what can be achieved by lowering lipid concentrations. CANTOS further showed a 31% reduction in cardiovascular 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 ACA and AHA recommendations are significantly more liberal in this context. Having 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 welcomed. In this context, our results single out a group of 27 (13%) subjects with hsCRP values >3mg/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 hypertension and diabetes increased in the younger population, which poses a specific and growing therapeutic challenge (45). Also, the results of the INTERHEART (Effect of Potentially Modifiable Risk Factors Associated with Myocardial Infarction in 52 Countries) study showed that 9 traditional RFs represent 90% of the population risk for myocardial infarction, influence particularly upon young people, that are less aware of their RFs, and therefore would less participate in primary prevention programs (46,47).

A special 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 cardiovascular calculator probably will not be needed (49). However, MPs belong to the special part of the population which are, according to their professional obligations, especially exposed to the risk of developing CVD (22,23). They are mostly younger than 50 years and the global level tendency of prevention of CVD and preclinical atherosclerosis of the younger population should be implemented into their regular systematic examinations (45, 50).

Last but not least, multiple regression analysis showed that age and fibrinogen have the significant influence on the increase in hs-CRP values in the group of older than 40 years, while in younger people only BMI has such influence upon hs-CRP. These results are in accordance with recent published study data considering the relationship between inflammation and aging (30-31,33). It is particularly interesting that age has not significant influence on hs-CRP in younger people. This finding may be contributed 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).

**Conclusion**

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

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

Limitation of the study: Having in mind that recommendations for primary CVD prevention and systematic assessment of CV risk are applied in men over 40 years we divided the MP into two groups of the younger and the older than 40 years, members of the same military unit, similar socioepidemiological and economic characteristics. Our study is the first one in Serbia which has the aim to analyse the association of hs-CRP with traditional risk factors for coronary heart disease, but has some limitations considering
study population number and diversity (no females) that may influence upon the generalization of the obtained conclusions.

Declaration

Ethical Approval and Consent to participate
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.

Consent for publication
Not applicable.

Availability of supporting data
All data generated or analyzed during this study are included in this published manuscript.

Competing interests
None of the authors have any competing interests in the manuscript.

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Authors' contributions
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Table 1 Basic clinical and laboratory characteristics of the subjects. Values were presented as number (%) or median (interquartile range: 25-75\textsuperscript{th} percentile)

| Characteristic                       | Value       |
|--------------------------------------|-------------|
| Total number of males                | 205         |
| Age (years)                          | 39 (35-43)  |
| Smoking                              | 61 (29.7)   |
| Family anamnesis for CVD             | 43 (21.0)   |
| Alcohol                              | 18 (8.8)    |
| Cholesterol, mmol/L                  | 5.30 (4.56-6.13) |
| Cholesterol ≥ 5.2mmol/L              | 113 (55.1)  |
| Triglycerides, mmol/L                | 1.17 (0.78-1.74) |
| Triglycerides ≥ 1.7mmol/L            | 54 (26.3)   |
| HDL cholesterol, mmol/L              | 1.26 (1.11-1.50) |
| HDL ≥ 1.0 mmol/L                     | 26 (12.7)   |
| LDL cholesterol, mmol/L              | 3.33 (2.75-4.10) |
| LDL ≥3.4mmol/L                       | 93 (45.4)   |
| Glycaemia, mmol/L                    | 5.40 (5.10-5.80) |
| Sedimentation, %                     | 7.00 (5.00-10.00) |
| Creatinine, µmol/L                   | 81 (74.50-87.00) |
| Body height, cm                      | 181.00 (177.00-186.00) |
| Body mass, kg                        | 88 (78.75-96.05) |
| Waist circumference, cm              | 107.00 (100.00-113.50) |
| Waist circumference ≥102cm           | 144 (70.2)  |
| Body mass index (BMI), kg/m\textsuperscript{2} | 26.80 (24.80-28.70) |
| Overweight                           | 149 (72.7)  |
| Normal <24.9 kg/m\textsuperscript{2} | 56 (27.3)   |
| Arterial hypertension, ≥ 140/90 mmHg | 39 (19.0)   |
| Systolic pressure, mmHg              | 120 (120-130) |
| Diastolic pressure, mmHg             | 80 (80-80)  |
| Fibrinogen, g/L                      | 2.90 (2.40-3.40) |
| hs-CRP, mg/L                         | 0.80 (0.43-1.75) |
| Low risk <1mg/L                      | 120 (58.5)  |
Intermediate risk 1-3 mg/L 58 (28.3)
High risk ≥3mg/L 27 (13.2)

Table 2. The Systematic COronary Risk Evaluation (SCORE) risk for the individuals older than 40 years

| SCORE (%) | 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) |

Low risk SCORE <1% for 10-years risk of fatal cardiovascular disease (CVD); Moderate risk: SCORE ≥1% and <5% for 10-years risk of fatal CVD

Table 3. Clinical characteristics of participants. Values were presented as number (%) or median (interquartile range: 25-75\textsuperscript{th} percentile.)

| Age groups | ≤40 years (n = 126) | ≥40 years (n = 79) | p value |
|------------|---------------------|-------------------|---------|
| Years      | 36 (34-38)          | 44 (42-47)        | <0.001* |
| Total cholesterol, 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, 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, mmol/L | <3.4 | ≥3.4 | p value |
|------------|------|------|---------|
| 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 pressure, mmHg | 120.00 (120.00-125.00) | 130.00 (120.00-135.00) | <0.001* |
| Diastolic 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/m² | 26.40 (24.70-28.60) | 27.41 (25.72-29.77) | <0.001* |
| Normal <24.9 kg/m² | 41 (32.5) | 15 (19.0) | 0.050** |
| Overweight ≥25 kg/m² | 85 (67.5) | 64 (81.0) |  |

*- Mann-Whitney test; **- Chi-square test

Table 4. Category of relative risk for CVD based on hs-CRP levels. Values were presented as number (%).

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

*Chi-Square Tests

Table 5. Correlation of risk factors with hs-CRP values.

| Correlation coefficient* | p value |
|--------------------------|---------|
| Age                      | 0.266   | <0.001 |
| Total cholesterol        | 0.131   | 0.062  |
| Individual number of risk factors | Number of participants n (%) | Hs-CRP, mg/L median (IQR) | p value* | Correlation coefficient** |
|----------------------------------|-----------------------------|--------------------------|---------|--------------------------|
| 0                                | 54 (26.3)                   | 0.68 (0.40-1.15)         |         | r=0.206, p=0.003         |
| 1                                | 84 (41.0)                   | 0.79 (0.41-1.54)         | 0.037   |                          |
| 2                                | 50 (24.4)                   | 1.16 (0.55-2.92)         |         |                          |
| 3                                | 16 (7.8)                    | 1.22 (0.59-2.65)         |         |                          |
| 4                                | 1 (0.5)                     | 3.77 (-)                 |         |                          |

IQR - interquartile range: 25-75th percentile; n (%) - number (%); *- Kruskal-Wallis test; **- Spearman's rank correlation coefficient

Table 6. Correlation of the individual number of risk factors with hs-CRP values

Table 7. Clinical and laboratory characteristics of the subjects according to hs-CRP value. Values were presented as number (%) or median (interquartile range: 25-75th percentile).
| Variable                        | Lower Limit (Mean) | Upper Limit (Mean) | P-value       |
|--------------------------------|--------------------|--------------------|---------------|
| 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-)       | 0.633*        |
| Fibrinogen, g/L                | 2.80 (2.30-3.30)   | 3.40 (2.80-3.70)   | <0.001*       |
| Systolic pressure, mmHg        | 120.00 (120.00-130.00) | 120.00 (120.00-130.00) | 0.220*       |
| Diastolic pressure, mmHg       | 80.00 (80.00-80.00) | 80.00 (80.00-85.00) | 0.131*        |
| Arterial hypertension ≥140/90mmHg | 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 cm                        | 54 (33.5)          | 7 (15.9)           | 0.030**       |
| ≥102 cm                        | 107 (66.5)         | 37 (84.1)          |               |
| Body mass index, kg/m²         | 26.50 (24.55-28.34) | 27.63 (26.00-31.10) | 0.004*        |
| Normal <24.9 kg/m²             | 53 (29.8)          | 3 (11.1)           | 0.043**       |
| Overweight ≥25 kg/m²           | 125 (70.2)         | 24 (88.9)          |               |

*- Mann-Whitney test; **- Chi-square test
Table 8. Univariate and multivariate linear regression analysis of assessment the importance of each independent variable in predicting or influencing hs-CRP

| Independent variables | <40 Independent variables | ≥40 Independent variables |
|-----------------------|---------------------------|---------------------------|
|                       | Linear regression analysis |                           |
|                       | Univariate analysis        | Multivariate analysis     |
|                       | Beta | p value | Beta | p value | Beta | p value |
| Age                   | 0.143 | 0.110  | 0.050 | 0.602  |
| Cholesterol           | 0.081 | 0.367  |
| Triglycerides         | 0.019 | 0.832  |
| HDL                   | -0.094 | 0.298 | -0.075 | 0.414  |
| LDL                   | 0.127 | 0.161  |
| Fibrinogen            | 0.216 | 0.021  | 0.183 | 0.057  |
| BMI                   | 0.274 | 0.002  | 0.240 | 0.012  |
| Systolic pressure     | 0.035 | 0.698  |
| Diastolic pressure    | 0.055 | 0.547  |
| Arterial hypertension | -0.032 | 0.722 | -0.0.65 | 0.485  |
| Age                   | 0.264 | 0.019  | 0.190 | 0.030  |
| Cholesterol           | -0.041 | 0.717  |
| Triglycerides         | 0.198 | 0.080  |
| HDL                   | -0.240 | 0.033 | -0.169 | 0.145  |
| LDL                   | -0.044 | 0.705  |
| Fibrinogen            | 0.069 | 0.561  | 0.269 | 0.026  |
| BMI                   | 0.132 | 0.248  | -0.093 | 0.453  |
| Systolic pressure     | 0.086 | 0.453  |
| Diastolic pressure    | 0.145 | 0.206  |
| Arterial hypertension | 0.225 | 0.048  | 0.199 | 0.093  |
hs-CRP is dependent variable; Multivariate analysis in group <40 years: F=2.917, p=0.017, R square 12.0%; Multivariate analysis in group >40 years: F=3.678, p=0.005, R square 21.8%