Acta Clin Croat 2024; 63:769-777

doi: 10.20471/acc.2024.63.03-04.38

Original Scientific Paper

MILD COGNITIVE IMPAIRMENT AND CARDIOMETABOLIC RISK FACTORS IN BOSNIAN AND HERZEGOVINIAN PATIENTS WITH HEART FAILURE

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SUMMARY — The aim of the present study was to assess mild cognitive impairment (MCI) and cardiometabolic risk factors (CMRF) in Bosnian and Herzegovinian patients with heart failure (HF). This study included 80 patients with HF and 40 healthy controls. Montreal Cognitive Assessment (MoCA) testing was used to evaluate cognitive function. Abdominal obesity was assessed by waist circumference, and hypertension was assessed by the auscultatory method. Data on other CMRF and comorbidities, such as diabetes, smoking, alcohol consumption, and atrial fibrillation (AF), were gathered with a specially designed questionnaire. Lipids, C-reactive protein (CRP), and fibrinogen were assessed with standard laboratory methods. Student, Mann-Whitney, and Chi-square tests were used to determine significant differences between groups. Associations between categorical variables and correlation coefficients were assessed by the Chi-square and Spearman test, respectively. The prevalence of MCI in patients with HF was 77.5%. We found significant associations between MCI and diabetes, hypertension, AF, and smoking in patients with HF. We found no significant associations between MCI, abdominal obesity, and alcohol consumption. A significant positive correlation between MCI and total cholesterol was observed in patients with HF. Furthermore, a lower MoCA score was associated with higher values of CRP and fibrinogen in HF patients. The present study showed a high prevalence of MCI in Bosnian and Herzegovinian HF patients as well as its association with various CMRFs. These results suggest it is necessary to begin MCI screening in HF patients, especially since data from the literature point to improvement in cognitive performance with appropriate HF and concomitant CMRF treatment.

Keywords: *Mild cognitive impairment*; *Cardiometabolic risk factors*; *Heart failure*

Introduction

Heart failure (HF) is one of the leading causes of mortality and one of the most frequent diagnoses in contemporary medicine. The prevalence of HF is rising due to an aging population[1]. Heart failure accounts for 80% of hospitalizations among individuals

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Received April 24, 2024, accepted September 15, 2024

over the age of 65[2]. The course of HF is progressive and negatively influences functional capability and quality of life, leads to frequent hospitalizations, and is associated with high mortality. HF represents a major clinical, economic, and public healthcare burden with a prevalence of more than 23 million cases worldwide[2].

Mild cognitive impairment (MCI) is defined as symptomatic predementia and is characterized by cognitive impairments not typical of healthy aging. Its main features are objective declines in cognitive functioning affecting attention, memory, and impairment in cognitive performance, unexpected for age and degree of education. However, individuals with MCI still do not require assistance in daily activities[3]. The factors that affect the progression of MCI to dementia are those that decrease cognitive reserve and include cerebrovascular events, lower levels of education, and accelerated neurodegenerative processes[4]. Although MCI is often regarded as a transitional phase between normal cognitive functioning and dementia, individuals with MCI – especially those of advanced age – are at a higher risk for the development of dementia[5].

The pathogenic mechanisms of cognitive impairment (CI) in patients with HF are not fully understood. It is believed that CI develops as a consequence of structural changes in the brain cortex and white matter due to microemboli from possible left ventricle thromboses, chronic or intermittent hypoperfusion due to low cardiac output secondary to left ventricle dysfunction, as well as to disturbed flow regulation in small blood vessels that lead to ischemic brain injury[6]. Impairment in blood-brain barrier function, oxidative stress, and inflammatory cytokines are also regarded as a link between HF and CI[3]. HF adversely affects various cognitive domains: attention, learning ability, working memory, and executive functions. Episodic memory of personal events and experiences, one of the most vital cognitive functions, is gradually distorted in patients with HF[7].

Cognitive impairment in patients with HF is often accompanied by various cardiometabolic risk factors (CMRF) and other comorbidities, such as diabetes mellitus, hypertension, obesity, atrial fibrillation (AF), coronary artery disease, anemia, depression, and sleep disorders. Studies have shown that these comorbidities have adverse effects on cognition and that improvement in these risk factors may ameliorate CI in patients with HF[1]. Moreover, studies have shown that race and ethnicity may affect outcomes in HF[8]. We therefore sought to assess MCI and CMRF in Bosnian and Herzegovinian patients with HF.

Materials and Methods

Study design and participants

The present study was a cross-sectional, clinical, comparative-descriptive study, and was conducted from March to December 2019 at Prim. Dr. Abdulah Nakaš General Hospital in Sarajevo, Bosnia and Herzegovina. The study included patients with HF who were hospitalized for HF treatment. The control group consisted of apparently healthy subjects based on objective and subjective parameters of general health condition and had no manifest signs of the disease. Patients with acute myocardial infarction, stroke, Parkinson's disease, multiple sclerosis, and malignancies were excluded from the study. Internal medicine specialists using New York Heart Association (NYHA) guidelines established a diagnosis of HF[9]. The left ventricle wall thickness and the ejection fraction were measured with the cardiac ultrasound real-time pro VIVID 4[10].

Ethical aspects of the study

The study protocol was approved by the Medical Ethics Committee at the site hospital (Ethical approval number 255-25/15). The study protocol was explained to all subjects in detail, and all subjects gave informed consent. All study procedures were performed following the Helsinki Declaration as revised in 2013.

Blood pressure and anthropometric measurements

Arterial blood pressures (expressed as mmHg) were measured in the left arm with mercury manometers by the standard Korotkoff auscultatory method after 5 minutes of rest. Anthropometric measurements included body weight (kg), body height (cm), and waist circumference (cm). Based on the waist circumference (WC), subjects were divided into those with and

without abdominal obesity according to International Diabetes Federation guidelines: WC ≥94 cm for men and ≥80 cm for women of European descent[11]. Data on other CMRFs and comorbidities, such as diabetes, smoking, alcohol consumption, and AF, were gathered through a questionnaire designed for this study.

Blood assay methods

Blood samples from subjects were drawn from antecubital veins after 12 hours of fasting. Following coagulation and centrifugation, the extracted serum was used in routine laboratory assessment of hematological and biochemical parameters. All biochemical analyses were performed in-house. Total cholesterol (TC), triglycerides (TG), and HDL-cholesterol (HDL-C) were assayed by standard enzymatic colorimetric techniques on automated machines (Dimension RxL Max, Dade Behring, Germany). The Friedewald formula was used to calculate LDL-cholesterol (LDL-C) levels[12]. Serum C-reactive protein (CRP) was determined by means of particle-enhanced immunonephelometry (BN Systems, Dade Behring, Marburg, Germany). The reference range for this method is 0-5 mg/L. Fibrinogen was measured by the turbidimetric method (AMS Fotometer FT2, AMS Analyzer Medical System). The reference range for this method is 1.9-3.9 g/L. Fasting glucose was determined by the glucose oxidase method. The normal range for this method is 3.3-6.1 mmol/L.

Assessment of cognitive function

Montreal Cognitive Assessment (MoCA) testing was used to evaluate cognitive functioning and to screen for MCI. MoCA evaluates episodic memory, language, attention, orientation, visuo-constructional and executive functions, as well as abstract thinking. The total possible score is 30. A score of ≥26 is considered normal, and a score between 18 and 26 is regarded as MCI[13].

Statistical analyses

Depending on distribution, Student's t-test or the Mann-Whitney U test were used to evaluate significant differences between the control and HF groups. The Chi-square test was used to test for the association of categorical variables, and Spearman's rank correlation coefficient was used to evaluate the strength and direction of continuous variables. Statistical significance was set to $P < 0.05$. All statistical procedures were performed in the Statistical Package for Social Sciences (SPSS; Chicago, Illinois, USA, version 19.0).

Table 1. Baseline characteristics of subjects included in this study

Variables	**Control group** n=40	**HF group** n=80	**P**
Age (years)	69.65 ± 6.97	72.58 ± 6.11	**0.02**
Sex (male /female) (%)	(55/45)	(51.2/48.8)	0.698
Heart rate (beats per minute)	72.50 (67.00-79.75)	71 (64.25-84.25)	0.684
Systolic blood pressure (mmHg)	150 (130-160)	155 (135-170)	0.289
Diastolic blood pressure (mm/Hg)	80 (70-90)	80 (70-90)	0.299
Fasting glucose (mmol/l)	5.70 (5.03-6.80)	6.10 (4.90-9.53)	0.212
Total cholesterol (mmol/L)	5.00 (4.50-5.90)	5.50 (4.10-6.20)	0.305
Triglycerides (mmol/L)	1.55 (1.24-1.88)	1.80 (1.30-2.10)	0.269
LDL-cholesterol (mmol/L)	1.65 (1.20-2.10)	2.95 (1.50-2.90)	**0.003**
HDL-cholesterol (mmol/L)	1.40 (1.20- 1.60)	1.50 (1.30-1.80)	0.208
C-reactive protein (mg/L)	4.00 (2.00-5.00)	12.00 (6.00-33.85)	**0.001**
Fibrinogen (g/L)	3.00 (2.26-3.90)	3.10 (3.00-4.00)	0.171
Education (elementary/high school /university) (%)	(7.5/57.5/35)	(17.5/68.8/13.8)	**0.017**

Data are shown as mean ± standard deviation, percentages, and median and interquartile range. HF = heart failure; P = probability

Results

In the present study, 120 subjects of both sexes, aged ≥ 60 years (80 subjects with HF and 40 control subjects) were enrolled.

As shown in Table 1, subjects with HF were older than controls (P=0.02), had higher values of LDL-C (P=0.003) and CRP (P=0.001), and had lower levels of education (P=0.017). We found no difference between subjects with HF and controls in sex, heart rate, blood pressure, fasting glucose, total cholesterol, triglycerides, HDL-cholesterol, or fibrinogen.

The median MoCA score in the control group was 27.50 (27.00-28.00), while among patients with HF, the MoCA score was 20.00 (19.00-24.50). The difference in MoCA scores between the control group of subjects with HF was statistically significant (P<0.001) (Figure 1).

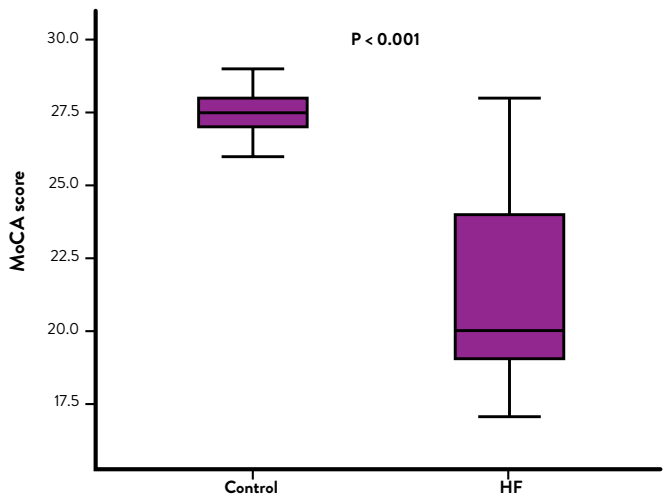

Figure 1. Box-and-whisker plot of Montreal Cognitive Assessment score in the study groups

The solid horizontal lines denote the median, the box represents the 25% and 75% interquartile ranges, and the whiskers represent the minimum and maximum values. HF = heart failure; P = probability

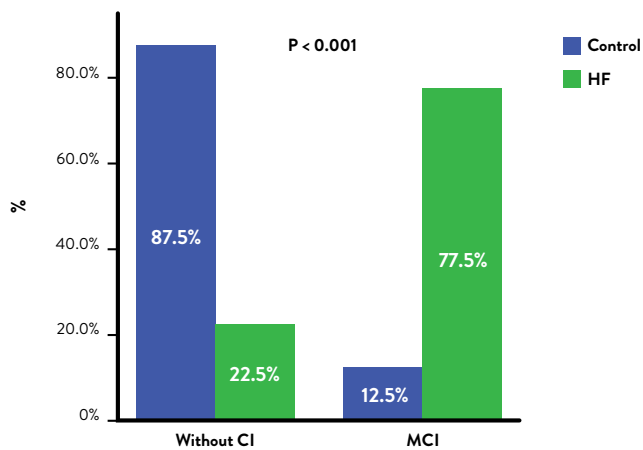

Figure 2. The prevalence of mild cognitive impairment in the control group and patients with heart failure.

HF = heart failure; CI = cognitive impairment; MCI = mild cognitive impairment

Table 2. The prevalence of standard cardiometabolic risk factors between control subjects and patients with heart failure

Cardiometabolic risk factors		**Control group n=40**	**HF group n=80**	**P**
Abdominal obesity (yes/no)	(n) (%)	(37/3) (92.5/7.5)	(72/8) (90/10)	0.750
Diabetes mellitus type 2 (yes/no)	(n) (%)	28/12 (70/30)	(58/22) (72.5/27.5)	**0.001**
Hypertension (yes/no)	(n) (%)	28/12 (70/30)	(77/3) (96.2/3.8)	**0.001**
Atrial fibrillation (yes/no)	(n) (%)	(1/39) (2.5/97.5)	(16/64) (20/80)	**0.010**
Smoking (yes/n)	(n) (%)	(20/20) (50/50)	48/32 (60/40)	0.297
Alcohol(yes/no)	(n) (%)	(8/32) (20/80)	(15/65) (18.8/81.2)	0.870

Data are shown as percentages. The difference between the groups was assessed by the Chi-square test. HF = heart failure

Table 3. Associations between mild cognitive impairment and standard cardiometabolic risk factors in control subjects and patients with heart failure

Risk factors			**Control group (n=40) Mild cognitive impairment**		**HF group (n=80) Mild cognitive impairment**	
			No n (%)	**Yes n (%)**	**No n (%)**	**Yes n (%)**
AO	**No**	**n (%)**	3 (8.6)	0 (0)	5 (27.8)	3 (4.8)
	Yes		32 (91.4)	5 (100)	13 (72.2)	59 (95.2)
	P		1.00		0.12	
DMT2	**No**	**n (%)**	25 (71.4)	3 (60)	14 (77.8)	8 (12.9)
	Yes		10 (28.6)	2 (40)	4 (22.2)	54 (87.1)
	P		0.627		**0.001**	
HT	**No**	**n (%)**	11 (31.4)	1 (20)	3 (16.7)	0 (0)
	Yes		24 (68.6)	4 (80)	15 (83.3)	62 (100)
	P		1.00		**0.01**	
AF	**No**	**n (%)**	35 (100)	4 (80)	18 (100)	46 (74.2)
	Yes		0 (0)	1 (20)	0 (0)	16 (25.8)
	P		0.125		**0.017**	
Smoking	**No**	**n (%)**	18 (51.4)	2 (40)	13 (72.2)	19 (30.6)
	Yes		17 (48.6)	3 (60)	5 (27.8)	43 (69.4)
	P		1.00		**0.002**	
Alcohol	**No**	**n (%)**	27 (77.1)	5 (100)	16 (88.9)	49 (79)
	Yes		8 (22.9)	0 (0)	2 (11.1)	13 (21)
	P		0.563		0.500	

HF = heart failure; AO = abdominal obesity; DMT2 = diabetes mellitus type 2; HT = hypertension; AF = atrial fibrillation; P = probability

Of the subjects included in this study, 77.5% of patients with HF and 12.5% of control subjects reached criteria for MCI, while in 22.5% of patients with HF and 87.5% of control subjects no cognitive impairment was evident. The difference in prevalence of MCI between the two groups was statistically significant on Chi-square testing (P<0.001) (Figure 2).

As shown in Table 2, statistically significant differences in CMRFs existed between patients with HF and control subjects. Subjects with HF were more likely to have diabetes mellitus (P=0.001), hypertension (P=0.001), and AF (P=0.010). We found no significant difference in abdominal obesity, smoking, or alcohol consumption between groups.

As shown in Table 3, statistically significant associations were determined between MCI and diabetes mellitus type 2 (P=0.001), hypertension (0.01), AF (P=0.017), and smoking (P=0.002) in patients with HF, while significant associations between MCI, abdominal obesity, and alcohol consumption were not found. In control subjects, significant associations were not determined between MCI and any CMRF.

As shown in Table 4, a statistically significant positive correlation was found between MCI and total cholesterol (P=0.012) in patients with HF, while correlations between MCI and other lipid indices were not established. In the control group, there were no significant correlations between MCI and any of the lipid indices. Moreover, results have shown that lower MoCA scores were associated with higher C-reactive protein (P=0.001) and fibrinogen (P=0.001) values in patients with HF. In the control group, lower MoCA scores were also associated with higher C-reactive protein (P=0.02) and fibrinogen (P=0.015) values.

Discussion

To the best of our knowledge, this is the first study to evaluate MCI and CMRFs in Bosnian and Herzegovinian patients with HF. Earlier studies have shown that ethnicity affects the prevalence, mechanisms, and outcomes of HF in the United Kingdom and Europe[14]. Novel studies have shown that, especially in Black and Hispanic patients, socioeconomic, environmental, and other public health determinants may be regarded as independent risk factors for HF and lead to poor outcomes[8]. The prevalence of MCI in our sample of patients with HF was 77.5%, which agrees with previous studies reporting a worldwide CI prevalence ranging from 31% to 85%[1] including patients of European descent. In this study, we used the MoCA test, which has better sensitivity but equal specificity for MCI than the Mini-Mental State Exam (MMSE), another frequently used test to assess cognitive function[15].

The observed high prevalence of MCI in HF patients calls for MCI screening in these patients, since it has been documented that CI significantly affects patients' ability to adhere to complex treatment. This may result in worsening of both HF and MCI and creates the possibility for a vicious and worsening disease cycle. Although the link between CI and HF remains elusive, these two conditions significantly affect each other. Studies have shown that the degree of CI correlates with HF severity[3]. In patients hospitalized for decompensated HF, cognition can be enhanced with improvement in left ventricular ejection fraction, which supports the concept of reversible CI in patients with acute HF and/or heart decompensation[6]. Moreover, HF patients are prone to a sedentary lifestyle and

Table 4. Correlations of mild cognitive impairment as assessed by Montreal Cognitive Assessment with lipid indices, C-reactive protein, and fibrinogen in control subjects and patients with heart failure

Groups	**Variables**	**TC (mmol/L)**	**TG (mmol/L)**	**LDL-C (mmol/L)**	**HDL-C (mmol/L)**	**CRP (mg/L)**	**FG (g/L)**
Controls	MoCA score	Rho=-0.123 P=0.451	Rho=-0.059 P=0.716	Rho= 0.189 P=0.244	Rho=-0.148 P=0.361	Rho= -0.366 **P=0.02**	Rho=-0.381 **P=0.015**
HF group		Rho=0.280 **P=0.012**	Rho=0.129 P=0.256	Rho=0.062 P=0.584	Rho=0.065 P=0.567	Rho= -0.502 **P=0.001**	Rho= -0.395 **P=0.001**

HF = heart failure; TC = total cholesterol; TG = triglycerides; LDL-C = LDL-cholesterol; HDL-C = HDL-cholesterol; CRP = C-reactive protein; FG = fibrinogen; Rho = Spearman correlation coefficient; P = probability

a lack of physical activity that worsens their primary disease[16].

Although previous studies have reported independent associations between CI and HF, comorbidities and CMRFs often accompany HF and may worsen cognitive impairment in these patients[17]. In the present study, statistically significant differences between patients with HF and control subjects were determined in the prevalence of standard comorbidities and CMRFs, such as diabetes mellitus, hypertension, and AF, while significant differences in the prevalence of abdominal obesity, smoking, and alcohol consumption were not found. Furthermore, our results have shown significant associations between MCI and diabetes mellitus type 2, hypertension, AF, and smoking in patients with HF, while significant associations between MCI, abdominal obesity, and alcohol consumption were not found. In the control subjects, significant associations were not found between MCI and any CMRF. However, it is of note that our controls had high values of blood pressure, which implies that hypertension remains undetected in seemingly healthy individuals.

The observed association between MCI and CMRF in HF patients may be explained by cerebral atrophy induced by hypoperfusion, blood vessel damage due to diabetes mellitus and hypertension, and brain infarction caused by microemboli[6,17]. A recent study by Lu *et al.*[18] reported that the elderly with a higher burden of cardiometabolic and vascular disease risk factors have an increased risk of CMI and dementia. AF may represent another possible link between MCI and HF since studies have demonstrated that patients with HF and AF have poorer cognitive abilities than HF patients without AF[1]. However, the interplay between MCI, HF, and AF is still not fully understood and requires additional investigation.

The present study demonstrated positive correlations between MCI and TC but not with other lipid indices in patients with HF. Moreover, results have shown that lower MoCA scores were associated with higher C-reactive protein (a pro-inflammatory CMRF) and fibrinogen (a pro-thrombotic CMRF) values in patients with HF. Interestingly, in the control group, lower MoCA scores were also associated with higher C-reactive protein and fibrinogen values. Earlier studies have shown that higher levels of CRP are associated with poorer executive and global cognitive functions in the elderly. However, based on current assumptions, CRP and other systemic markers of inflammation are not appropriate in CI risk stratification[19]. As for fibrinogen, findings suggest that it has a causative role in neurodegeneration and neuroinflammation. Pyun *et al.*[20] have recently reported that in patients with MCI, fibrinogen is associated with worse performance in attention, regardless of vascular risk factors or apolipoprotein E (APOE) genotype.

Although this study is the first to assess MCI and CMRF in Bosnian and Herzegovinian patients with HF, it also has several limitations. First, because of its cross-sectional design, cause and effect cannot be determined. Second, our sample study was relatively small and consisted solely of hospitalized patients with HF, so these results might not be generalizable to wider populations. Third, MoCA testing was used to assess for MCI, and it is possible that the use of other tests in the evaluation of cognitive functions might yield differing results. Fourth, HF patients were not stratified according to NYHA HF functional classifications. Finally, it is necessary to emphasize possible bias in our results, since significant differences were determined in age and education level between patients with HF and controls. Age and education level are known risk factors for CI and future similar studies would benefit from avoiding this potential source of bias. Other confounding factors that might be related to MCI in the HF hospitalized cohort should also be considered by future studies.

Conclusion

The present study showed a high prevalence of MCI in Bosnian and Herzegovinian HF patients, as well as its association with various CMRFs. Since CI may influence activities of daily living and adherence to treatment in patients with HF, our results suggest clinicians should begin MCI screening promptly in HF patients, especially since data from the literature point to cognitive improvement with appropriate and concomitant HF and CMRF treatment.

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Sažetak

BLAGI KOGNITIVNI POREMEĆAJ I KARDIOMETABOLIČKI ČIMBENICI RIZIKA KOD BOSANSKOHERCEGOVAČKIH PACIJENATA SA ZATAJIVANJEM SRCA

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Cilj je ovog istraživanja bio procijeniti blagi kognitivni poremećaj (BKP) i kardiometaboličke čimbenike rizika (KMČR) u bosanskohercegovačkih pacijenata sa zatajivanjem srca (ZS). U ovo je istraživanje uključeno 80 pacijenata sa ZS-om i 40 zdravih kontrolnih ispitanika. Kognitivne funkcije evaluirane su testiranjem Montrealskom kognitivnom procjenom (MoKP). Abdominalna pretilost procijenjena je opsegom struka, a hipertenzija auskultatornom metodom. Podaci o ostalim KMČR-ima i komorbiditetima, poput dijabetesa, pušenja, konzumacije alkohola, kao i atrijalne fibrilacije (AF), prikupljeni su pomoću posebno izrađenog upitnika. Lipidi, C-reaktivni protein (CRP) i fibrinogen procijenjeni su standardnim laboratorijskim metodama. Za utvrđivanje statistički značajnih razlika između skupina korišteni su Studentov t-test, Mann-Whitneyjev U test i χ^2- test. Povezanosti između kategoričkih varijabli i koeficijenti korelacije procijenjeni su χ^2-testom, odnosno Spearmanovim testom. Prevalencija BKP-a u pacijenata sa ZS-om iznosila je 77.5%. Utvrđena je značajna povezanost između BKP-a i dijabetesa, hipertenzije, AF-a i pušenja u pacijenata sa ZS-om. Nismo utvrdili značajnu povezanost između BKP-a, abdominalne pretilosti i konzumacije alkohola. Značajna pozitivna korelacija između BKP-a i ukupnog kolesterola uočena je u pacijenata sa ZS-om. Nadalje, niži MoKP rezultat bio je povezan s višim vrijednostima CRP-a i fibrinogena u pacijenata sa ZS-om. Ovo je istraživanje pokazalo visoku prevalenciju BKP-a u bosanskohercegovačkih pacijenata sa ZS-om, kao i njegovu povezanost s različitim KMČR-ima. Ovi rezultati upućuju na potrebu za uvođenjem probira na BKP u pacijenata sa ZS-om, posebice s obzirom da podaci iz literature ukazuju na poboljšanje kognitivne izvedbe uz odgovarajuće istodobno liječenje ZS-a i KMČR-a.

Ključne riječi: *Blagi kognitivni poremećaj*; *Kardiometabolički čimbenici rizika*; *Zatajivanje srca*