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Relationship between polymorphism rs2794521 in *CRP* gene and survival of depressive patients with chronic heart failure

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Abstract. – OBJECTIVE: Currently, there is a lack of studies combining the relationship between depression, chronic heart failure (CHF) and *CRP* polymorphisms (SNPs). The objective of the study was the investigation of the potential influence of rs2794521 in CRP on the survival and clinical profile of patients suffering from both depression and CHF.

PATIENTS AND METHODS: 103 CHF individuals were studied to evaluate depression occurrence and to compare values of cardiac, laboratory and nutritional parameters depending on CRP genotypes.

RESULTS: The higher frequency of CC genotype was found in depressive patients (p=0.021). Serum *CRP* concentration was significantly higher in depressed patients than in non-depressed ones (p=0.032). CC depressive individuals demonstrated greater frequency of NYHA grade III-IV (p<0.001) and higher level of circulating CRP (p=0.001) and TNF-α (p=0.042) compared with CT or TT carriers. CC individuals were more frequently classified as moderately or severely malnourished according to SGA (p=0.014). CC genotype was associated with a higher risk of early death during the 72 months of the follow-up (HR=4.01; p=0.006 for CC *vs.* CT *vs.* TT and HR=4.46; p<0.001 for CC *vs.* CT+TT).

CONCLUSIONS: CC genotype of CRP more frequently occurs in depressive CHF patients, and it is associated with worse clinical outcomes and disease prognosis.

Key Words:
Chronic heart failure, Single nucleotide polymorphisms (SNP), Depression, Inflammation, Nutrition, CRP.

Introduction

Depression is still serious clinical and socio-economic issue. The background of this disease in chronic diseases is still not fully understood. In recent years, particular attention has been paid to the correspondence between depression and inflammatory state[1]. The role of inflammatory cytokines in depression, such as TNF-α, IL-1β and IL-6 has been investigated for several years. This group of cytokines, as well as C-reactive protein (CRP), are potential mediators of communication between the brain and other parts of the body and trigger the aforementioned "sickness behavior" and depression[2,3].

A significantly higher level of CRP was found in patients with a positive family history[4]. It has to be emphasized that these individuals had only a diagnosis of depression, with or without positive family history. The researchers identified certain SNPs in *CRP* (A allele in rs1417938 and C allele in rs1205), which could up-regulate serum CRP level, and thus can be associated with depression occurrence. In another research[5], authors observed that the risk of depression was greater among patients with clinically significant depressive symptoms, who carry the rs1205 G/A of the CRP gene. It was associated with approximately 20% lower serum concentration of CRP[5]. Golimbet et al[6] studied the relationship between SNPs in genes encoding IL-4 (-589 C/T), IL-6 (-174 G/C), tumor-necrosis factor alpha (*TNF-α* -308 G/A) and CRP (-717A/G) and depression, comorbid to CHF. They found the association between the *IL-6* -174 G/C and depression comorbid to CHF (p=0.01; OR=2.3). The frequency of allele G in this group was higher compared to controls. The association between IL-4 -589 C/T and CHF was found. However, the association between the *TNF-α* -308G/A and the *CRP* -717A/G with depression in CHF was not observed. In another study, Kittel-Schneider et al[7] found the association of less

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common *CRP* genetic variants with depressive symptoms, which increased mortality risk and CRP level in the population of CHF patients. It suggests a possible role of the inflammatory system as a link between poor prognosis in CHF and depressive symptoms. Less common recessive genotypes of two SNPs in the *CRP* (rs1800947 and rs11265263) were observed. These were associated with significantly higher mortality risk (p<0.006), higher CRP serum level (p=0.029, p=0.006) and increased depressive symptoms.

Until now, there are a lack of studies among patients with CHF conducted on the issue, whether the occurrence of certain SNPs in *CRP* affects the patients' survival. Based on the above mentioned, this paper attempted to investigate the potential influence of the rs2794521 in *CRP* on the prognosis and clinical course of depression and heart failure.

Patients and Methods

Study Group

103 CHF individuals were screened for the presence of depression. Among study participants, depression was diagnosed in 66 individuals (64.1%), who were then enrolled in the study group. They were treated and followed up at the Department of Cardiology, Military Hospital in Lublin in Poland between 2015 and 2021. 37 of CHF non-depressed patients were enrolled as a control to compare rs2794521 genotype distribution between depressed and non-depressed patients. Guideline released by European Society of Cardiology was used for CHF detection and included assessment of echocardiographic diagnostics (left ventricular end-diastolic and end-systolic diameters – LVEDD and LVESD; ejection fraction – EF%; right ventricular outflow tract – RVOT; tricuspid annular plane systolic excursion – TAPSE and left anterior descending artery – LAD), New York Heart Association (NYHA) functional classification and laboratory tests (serum concentration of albumin, total cholesterol, triglycerides, creatinine, hemoglobin and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and inflammatory markers: serum CRP and TNF-α concentration). In Table I, the detailed clinical baseline features of the studied depressed CHF patients were summarized.

Laboratory and cardiac parameters were supplemented by anthropometrical measurements, which included body mass and body mass index (BMI) values. Subjective global assessment (SGA) and nutritional risk score index (NRS-2002) clinical questionnaires were applied for nutritional screening of patients. Evans et al[8] criteria were applied for cachexia detection. The defined exclusion and inclusion criteria were applied to study protocol – inclusion criteria: 1) depression confirmed by psychiatrist; 2) newly diagnosed CHF; 3) known medical history and availability of full clinical data; 4) signed informed consent

Table I. Baseline characteristics of the depressive CHF patients.

Factor		Study group (n=66)
Gender	**Male**	36 (54.5%)
	Female	30 (45.5%
Age ± **SD** (years)		73±13
Weight (kg)		80±19
BMI (kg/m^2)		28.78±6.20
FM (kg)		22.6±14.2
FFM (kg)		53.9±14.5
Albumin (g/dL)		3.52±0.57
Triglycerides (mg/dL)		104±56
Total cholesterol (mg/dL)		162±43
Creatinine (mg/dL)		1.27±0.56
Hemoglobin (g/dL)		13.0±1.8
CRP (mg/L)		18.4±14.8
TNF-α (pg/mL)		4.41±1.56
Systolic blood pressure (mmHg)		132±22
Diastolic blood pressure (mmHg)		75±14
EF%		42±14
NT-proBNP (pg/mL)		3772±3459
LVESd (cm)		4.2±1.0
LVEDd (cm)		5.2±1.2
LAD (cm)		4.5±0.7
RVOT (cm)		3.5±0.5
TAPSE (cm)		1.9±0.4
PASP (mmHg)		42±14
NYHA	**I**	14 (21.6%)
	II	20 (30%)
	III	16 (24.2%)
	IV	16 (24.2%)
SGA	**A**	32 (48.5%)
	B	22 (33.3%)
	C	12 (18.2%)
NRS	**<3**	41 (62.1%)
	≥3	25 (37.9%)
Diabetes mellitus		26 (39.4%)
Renal failure		19 (28.8%)
Smoking Status	**Smoker**	38 (57.6%)
	Non-smoker	28 (42.4%)

of patients, and exclusion criteria were as follows, 1) condition after the implantation of metallic implants or cardioverter defibrillator; 2) acute coronary syndrome or coronary artery bypass grafting within last 6 months; 3) hyperthyroidism or hypothyroidism) criteria were applied. Bioethical Commission in Medical University of Lublin (no of consent: KE-0254/64/2017) approved the study protocol.

Diagnosis of Depression

To screen depression and its symptoms as well as its severity we applied Beck Depression Inventory (BDI). All studied patients completed a multiple-choice 21-question (scored between 0 and 3 points) self-report inventory. Based on the achieved score, they were diagnosed as depressive symptomatic or non-depressed patients. The following cut-off point was applied to distinguish between symptomatic and non-depressed patients: BDI score ≥12 points (depression symptoms presented). All subjects with diagnosed depression were consulted by psychiatrist at hospital psychiatric ward in order to confirm initial diagnosis. Regarding achieved BDI score allowing to distinguish mild from moderate or severe depression and to qualify patients to studied subgroups, the BDI cut-off score was as follows: mild depression (12-19 points) and moderate or severe depression (over 20 points). Based on the mentioned criteria, 45 patients (68.2%) were diagnosed as mildly depressed and 21 (31.8%) as moderately or severely depressed.

Genotyping of rs2794521

Samples containing 200 µl of whole blood were used for DNA extraction by DNA Blood Mini Kit (Qiagen, Canada). Allele discrimination PCR method was used to genotype rs2794521 of CRP gene. The genotyping reaction was conducted in StepOnePlus PCR device (Applied Biosystems, Foster City, CA, USA) according to the manufacturer's protocol using Genotyping Master Mix and TaqMan probes specific for targeted SNP (Thermo Fisher Scientific, Waltham, MA, USA). The genotypes variants were obtained and analyzed on StepOne Software v2.3 (Applied Biosystems, Foster City, CA, USA).

Statistical Analysis

We applied MedCalc (version 15.3; MedCalc, Belgium) software for statistical analysis purposes. Chi-square test was used to compare genotype distribution between CHF patients. Differences in the values of studied parameters between patients carrying various genotypes of rs2794521 were tested by one-way analysis of variance (ANOVA) for continuous data and Chi-square test for dichotomous data. Log-rank test (univariate analysis) and Kaplan-Meier survival estimator were applied to assess factors affecting overall survival in the studied group. To investigate association between the survival of depressed CHF patients and all studied parameters, the Cox proportional hazards model was used. Both survival analysis provided hazard ratio (HR) with 95% Confidence Interval (95% CI) calculation. The results achieving $p<0.05$ were considered as significant.

Results

Genotype distribution of rs2794521 is summarized in Table II. Genotype distribution met Har-

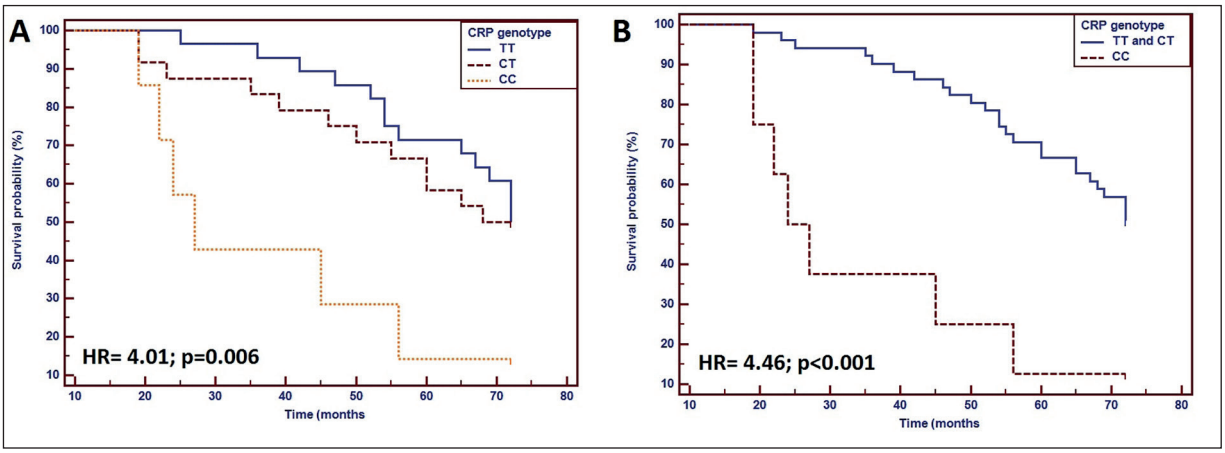

Figure 1. Impact of the rs2794521 genotypes on overall survival of depressed CHF patients: **A** – survival curves for CC, CT and TT genotype carriers; **B** – survival curves for CC and CT+TT genotypes

dy-Weinberg equilibrium (p=0.901). We noticed significant difference in genotypes distribution between depressive and non-depressive CHF patients, the higher frequency of CC and CT genotypes was found in depressive patients (p=0.021). Moreover, CRP concentration was significantly higher in depressed patients than in non-depressed ones (mean serum CRP concentration: 19.4±17.8 and 10.3±12.9 mg/L; p=0.032). We did not find differences in rs2794521 distribution between patients suffering from mild or more severe depression (p=0.327) as well as lack of differences in serum CRP level (p=0.798).

In Table III we demonstrated differences in the values of studied cardiac, laboratory and clinical parameters between different genotype carriers. As for cardiac measurements, we noticed significant reduction in EF% and LVEDD values between CC genotype carriers and other patients (mean EF%: 27±13 for CC and 41±12, 48±12 for CT and TT, respectively; p=0.002) (mean LVEDD: 5.8±1.0 cm for CC and 5.2±1.0 and 4.9±1.0 for CT and TT, respectively; p=0.019). Interestingly, CC depressive individuals demonstrated higher values of NT-proBNP (mean concentration for CC: 6289±2750 pg/mL, CT: 3350±2000 pg/mL and TT: 3267±2021 pg/mL; p=0.041) and greater frequency of NYHA grade III or IV (p<0.001). Regarding laboratory parameters, CC individuals demonstrated higher level of circulating inflammatory markers CRP (mean CRP: CC – 38.8±12.4 mg/L, CT – 15.98±16.2 mg/L and TT – 9.1±10.9 mg/L; p=0.001) and TNF-α (mean TNF-α: CC – 5.44±1.52 pg/mL, CT – 4.48±1.81 pg/mL and TT – 3.89±1.10 pg/mL; p=0.042), but lower hemoglobin (mean hemoglobin level: CC – 10.8±1.2 g/dL, CT – 13.1±1.7 g/dL and TT – 13.6±1.3 g/dL; p=0.001) and albumin (mean albumin concentration : CC – 3.10±0.47 g/dL, CT – 3.56±0.57 g/dL and TT – 3.77±0.40 g/dL; p=0.034) concentration comparing with CT or TT carriers. CC CHF individuals were more frequently classified as moderately or severely malnourished according to SGA questionnaire (SGA-B and SGA-C) (p=0.014).

The second goal of the study was to assess factors affecting survival in the group of depressed CHF patients. For this purpose, we conducted log-rank test analysis with Kaplan-Meier survival estimator followed by Cox proportional hazards model. During the follow-up period (72 months) 38 patients died (57.6% of the study group), the dead incidence was as follows, 70% in CC group, 60% in CT and 42.9% in TT group. Independent unfavorable factors affecting survival in the studied patients were as follows: NYHA grade III or IV (HR=1.92; p=0.033), CC genotype of rs2794521 (HR=4.01; p=0.006 for CC *vs.* CT *vs.* TT and HR=4.46; p<0.001 for CC *vs.* CT+TT)(Figure IA, IB), hemoglobin concentration below 12 g/dL (HR=2.14; p=0.028) and presence of severe depression (HR=3.92; p=0.037)(Table IV).

All studied clinical, cardiac, laboratory and nutritional measurements were introduced to Cox model. The factors significantly affecting overall survival in the studied patients were as follows: albumin concentration <3.2 g/dL (HR=10.22; p=0.0011), EF% <40 (HR=2.09; p=0.018), CC genotype of CRP (HR=3.79; p=0.022), NYHA grade III or IV (HR=2.09; p=0.036) and severe depression (HR=4.88; p=0.039) (Table V).

Table II. Distribution of rs2794521 genotypes among CHF patients depending on the depression diagnosis and disease severity.

Factor	Depression (n=66)	Non-depression (n=37)	p
CC	10 (15.2%)	3 (8.1%)	0.021
CT	32 (48.5%)	10 (27%)	
TT	24 (36.3%)	24 (64.9%)	
CRP (mg/L)	19.4±17.8	10.3±12.9	0.032
Factor	**Mild depression (n=45; 68.2%)**	**Moderate or severe depression (n=21; 31.8%)**	**p**
CC	5 (11.1%)	5 (23.8%)	0.327
CT	24 (53.3%)	8 (38.1%)	
TT	16 (35.6%)	8 (38.1%)	
CRP (mg/L)	17.2±12.1	19.4±9.7	0.798

Table III. The effect of liraglutide, methotrexate and combined administration of liraglutide with methotrexate on the gene expression levels of IL-1B, IL-6 and VEGF in cardiac tissue of methotrexate induced cardiotoxicity in rats.

Factor		CC (n=10; 15.2%)	CT (n=32; 48.5%)	TT (n=24; 36.3%)	p
Age±SD (years)		75±12	72±12	73±13	0.786
Gender	Male	6 (60%)	17 (53.1%)	13 (54.2%)	0.929
	Female	4 (40%)	15 (46.9%)	11 (45.8%)	
Systolic blood pressure (mmHg)		133±20	130±19	130±22	0.964
Diastolic blood pressure (mmHg)		72±11	78±15	73±12	0.334
EF%		27±13[a]	41±12[b]	48±12[b]	0.002
NT-proBNP (pg/mL)		6289±2750[a]	3350±2000[b]	3267±2021[b]	0.041
LVESD (cm)		4.8±0.5	4.2±1.0	4.1±0.9	0.338
LVEDD (cm)		5.8±1.0[a]	5.2±1.0b	4.9±1.0b	0.019
LAD (cm)		4.7±0.4	4.4±0.6	4.5±0.8	0.667
RVOT (cm)		3.5±0.7	3.5±0.5	3.4±0.5	0.886
TAPSE (cm)		1.9±0.7	1.8±0.4	1.8±0.4	0.539
PASP (mmHg)		43±18	40±12	42±16	0.730
NYHA	I	0	7 (21.9%)	7 (29.2%)	<0.001
	II	2 (20%)	6 (18.7%)	12 (50%)	
	III	1 (10%)	10 (31.3%)	5 (20.8%)	
	IV	7 (70%)	9 (28.1%)	0	
	I and II	2 (20%)	13 (40.6%)	19 (79.2%)	0.006
	III and IV	8 (80%)	19 (59.4%)	5 (20.8%)	
Diabetes mellitus	Yes	8 (80%)	9 (28.1%)	9 (37.5%)	0.013
	No	2 (20%)	23 (71.9%)	15 (62.5%)	
Renal failure	Yes	2 (20%)	9 (28.1%)	8 (33.3%)	0.732
	No	8 (80%)	23 (71.9%)	16 (66.7%)	
Smoking status	Smoker	5 (50%)	15 (46.9%)	17 (70.8%)	0.185
	Non-smoker	5 (50%)	17 (53.1%)	7 (29.2%)	
Weight (kg)		81±22	79±16	81±10	0.849
BMI (kg/m^2)		28.5±4.4	28.5±5.6	29.2±7.1	0.886
Albumin (g/dL)		3.10±0.47[a]	3.56±0.57[b]	3.77±0.40[b]	0.034
Triglycerides (mg/dL)		91±30	104±45	106±60	0.867
Total cholesterol (mg/dL)		150±63	155±40	170±41	0.379
Creatinine (mg/dL)		1.26±0.43	1.29±0.54	1.27±0.51	0.925
Hemoglobin (g/dL)		10.8±1.2[a]	13.1±1.7[b]	13.6±1.3[b]	0.001
CRP (mg/L)		38.8±12.4[a]	15.98±16.2[b]	9.1±10.9[b]	0.001
TNF-α (pg/mL)		5.44±1.52	4.48±1.81	3.89±1.10	0.042
Cachexia	Yes	6 (60%)	12 (37.5%)	7 (29.2%)	0.240
	No	4 (40%)	20 (62.5%)	17 (70.8%)	
NRS	<3	3 (30%)	22 (68.8%)	16 (66.7%)	0.075
	≥3	7 (70%)	10 (31.2%)	8 (33.3%)	
SGA	A	2 (20%)	11 (34.4%)	14 (58.3%)	0.035
	B	5 (50%)	12 (37.5%)	10 (41.7%)	
	C	3 (30%)	9 (28.1%)	0	
	A	2 (20%)	23 (71.9%)	14 (58.3%)	0.014
	B or C	8 (80%)	9 (28.1%)	10 (41.7%)	

Discussion

Currently, SNPs and their role in the development, progression and treatment of depression are in the interest of both clinicians and researchers. They pay attention to SNPs in genes encoding proteins involved in the mediation and progression of inflammation, such asIL-1, 6, CRP and TNF-α. These seem to be crucial for depressive disorders, but also for chronic diseases that often coexist with depression. High level of inflammatory markers has been noticed during depression[9]. It often coexists with circulatory failure, and the results of available studies underline, that in the patients suffering from depression there is a higher risk of cardiac failure and its more severe course (based on the NYHA), than in non-depressive individuals[10]. Kittel-Schneider et al[7] in their research concluded that genetic variants of *CRP* are associated with higher mortality with higher CRP concentration and increased depressive symptoms in CHF. In the mentioned paper, the carriers of the rare re-

Table IV. Factors affecting the overall survival of CHF individuals suffering from depression (log-rank test).

		Log-rank test (univariate analysis)	
Factor	**Median OS (months) (unfavorable *vs.* favorable)**	**HR [95%CI]**	***p***
CC *vs.* CT *vs.* TT	28 *vs.* 68 *vs.*72	4.01[0.88-18.37]	0.006
CC *vs.* CT+TT	28 *vs.* 70	4.46 [1.03-19.42]	<0.001
Hemoglobin <12 g/dL	55 *vs.*72	2.14 [0.95-4.80]	0.028
NYHA III or IV	52 *vs.* 72	1.92 [0.94-3.76]	0.033
Severe depression	56 *vs.* 70	3.92 [1.12-14.79]	0.037

Table V. Factors significantly affecting the overall survival of CHF individuals suffering from depression (Cox proportional hazards model).

Covariate	**HR [95%CI]**	***p***
Albumin <3.2 g/dL	10.22 [0.61-71.22]	0.011
EF%< 40	2.09 [0.99-4.21]	0.018
CC genotype vs. others	3.79 [1.03-12.82]	0.022
NYHA III or IV	2.09 [0.79-5.99]	0.036
Severe depression	4.88 [0.91-26.1]	0.039
	Overall model fit: p=0.019	

cessive genotypes (rs1800947 CC and rs11265263 AA) of the *CRP* scored significantly higher in the depression module of the PHQ-9 in comparison to the GG carriers, suggesting increased depressive symptoms in those patients. Additionally, the C allele of *CRP* rs1800947 and A allele of rs1126263 were associated with both increased mortality and grade of depressive symptoms measured by PHQ-9[7]. Our findings are partly similar. The higher frequency of CC and CT genotypes (rs2794521) of *CRP* were found more often in depressive patients (p=0.021). Similarly like in the cited study, also in our group of patients, CRP concentration was significantly higher in depressed individuals than in non-depressed subjects (mean serum CRP concentration: 19.4±17.8 and 10.3±12.9 mg/L; p=0.032). These findings are in contrast with the study of Dekker et al[11]. They did not find the relationship between concentration of inflammatory markers and manifestation of depressive symptoms. They suggested a lack of a relationship between depressive symptoms and inflammatory markers in CHF patients. In our study individuals with recessive CC genotype of *CRP* demonstrated higher concentration of NT-proBNP (p=0.041) and greater frequency of NYHA grade III or IV (p<0.001). Regarding laboratory parameters, CC individuals had higher level of circulating inflammatory markers: CRP (p=0.001) and TNF-α (p=0.042), but lower hemoglobin (p=0.001) and albumin (p=0.034) concentration comparing with CT or TT carriers. In some studies anemia has been presented to be an independent risk factor associated with unfavorable outcomes in CHF patients[12]. However, low concentration of hemoglobin has been recorded in another research as factor not related to depressive symptoms[13]. Moreover, a decreased hemoglobin concentration was noted in somatically unburdened depressed individuals[14]. Other studies[15,16] have demonstrated, that in cancer patients, the lower the hemoglobin level is detected, the higher the risk of depression exists[15,16].

Several papers support the correlation between high prevalence of depression in NYHA class II-IV with a greater level of cognitive dysfunction in class III/IV patients[17]. In the group of depressed individuals, the higher severity of depression (measured by BDI scale) is related to the lower EF%. It negatively affects the quality of life of patients[18]. Regarding our results, the factors, such as EF % and NYHA (III or IV), albumin concentration, CC genotype of *CRP* and severe depression affected overall survival of CHF patients, as follows: albumin concentration <3.2 g/dL (HR=10.22; p=0.0011), EF% <40 (HR=2.09; p=0.018), CC genotype of CRP (HR=3.79; p=0.022), NYHA grade III or IV (HR=2.09; p=0.036) and severe depression (HR=4.88; p=0.039). It should be noted that elevated inflammatory cytokines concentration can trigger depressive symptoms or the

severe HF symptoms themselves. However, to which amount the depression accounts for the elevated level of CRP and by this way effect cognitive dysfunction is still unclear. In the studied group, the concentration of TNF-α was definitely the highest in CC homozygotes, and the lowest in TT genotype group (5.44 ± 1.52 pg/mL *vs.* 3.89 ± 1.10 pg/mL; p=0.042). The level of TNF-α in depressed atientswas described in several papers as higher than in the control group, so far[19,20]. The above results seem to confirm the potential influence of rs2794521 in CRP gene as well as CRP concentration on the clinical image of both depression and heart failure.

In patients with diagnosed depression, we probably could find a higher susceptibility to the development of cachexia. In the literature, we can find few data indicating a correlation of cachexia with a deeper degree of depression and, at the same time, worse quality of life. However, the study[18] was carried out on a group of subjects with simultaneous oncological diagnosis. Regarding our study, we recorded the lowest concentration of albumin in CC genotype group (p=0.034) and found that albumin concentration <3.2 g/dL (HR=10.22; p=0.0011) was the risk factor of overall survival reduction. We could predict that in carriers of the CC genotype malnutrition and/or cardiac cachexia may develop.

Conclusions

In this publication the presence of the CC genotype of CRP gene in patients with depression with CHF together with EF%, NYHA III or IV, albumin concentration, and severe depression can be considered as unfavorable prognostic factors related to the overall survival. Therefore, carriers of the CC genotype suffering from CHF and depression should receive special cardiological, nutritional and psychiatric care in order to achieve similar therapeutic benefits as in patients without severe inflammation. However, the above observation requires further and more scrupulous studies on larger groups of patients.

Conflicts of Interest

The authors declare no conflicts of interest.

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