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Effect of polymorphism rs1799964 in TNF-α gene on survival in depressive patients with chronic heart failure

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Abstract. – OBJECTIVE: To date, there are no literature reports combining the relationship between depression and chronic heart failure (CHF) in relations to selective nutritional, cardiac and laboratory parameters. The aim of this study was to correlate the rs1799964 genotypes in TNF-α with clinical outcomes of depressive CHF patients.

PATIENTS AND METHODS: 94 CHF patients were enrolled to assess depression prevalence and to compare values of cardiac, laboratory and nutritional parameters between depressed and non-depressed patients with different rs1799964 genotypes.

RESULTS: Depression was diagnosed in 66 individuals (70.2%). We noted significant reduction of EF% in CC genotype carriers compared to other patients (mean EF%: 36±11 CC vs. 44±14 CT and 46±7 TT; *p*=0.023) and worse outcomes in NYHA examination (*p*=0.033). We noticed a significant increase in serum CRP and TNF-α in CC patients (*p*=0.003 and *p*<0.001). Compared with T allele carriers, the CHF patients bearing CC genotype were more frequently diagnosed as cachectic (cachexia incidence for CC – 80% vs. 28% for CT and 38.7% for TT; *p*=0.017). CC genotype of rs1799964 was found as unfavorable factor affecting survival of depressive CHF patients (HR=8.87; *p*<0.001).

CONCLUSIONS: The presence of the CC genotype in patients with depression and CHF can be considered an unfavorable prognostic factor related to the risk of shortening the life expectancy and deteriorating its quality, which is reflected in the severity of inflammation.

Key Words:

Chronic heart failure, Single nucleotide polymorphism, Depression, Inflammation, Nutrition.

Abbreviations

BDI - Beck Depression Inventory; BIA – bioelectrical impedance analysis; BMI – body mass index; CHF – chronic heart failure; EF% - ejection fraction; LAD - left anterior descending artery; NYHA – New York Heart Association; RVOT - right ventricular outflow tract; SGA – subjective global assessment; TAPSE - tricuspid annular plane systolic excursion.

Introduction

Depression is a growing clinical, social and economic problem. The etiology of this disorder, especially in chronic diseases is still not fully understood. In recent years, particular attention has been paid to the relationship between depression and inflammatory response[1].

Inflammatory factors, taking effect through the kynurenine pathway, reduce the levels of serotonin and melatonin, and thus can trigger depression[1,2]. Therefore, it appears as the result of too intense or too long-lasting immunological excitation, and biochemically it is the activation of the kynurenine pathway that is responsible for the transition from "sickness behavior" to depression[3].

The role of =cytokines in depression, such as TNF-α, IL-1β, and IL-6, has been discussed for several years. This group of cytokines, especially IL-6 and CRP is assigned the role of potential mediators of communication between the brain and other parts of the body and triggering the aforementioned "sickness behavior" and depression[4] . Bialek et al[5] found, that there are polymorphisms in IL-1 α, IL-1β and TNF-α genes which are correlated with the occurrence, severity and treatment outcomes. Five polymorphisms: (c.-1560G>C - IL-1β (rs1143623), c.-118C>T - IL-1β (rs1143627), c.340G>T - IL-1α (rs17561), c.-1211T>C - TNF-α (rs1799964) and c.488G>A - TNF-α (rs1800629) were found to be associated with a disease seve-

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rity and they can affect the effectiveness of antidepressant therapy. Additionally, these SNPs may modulate the risk of depression[5]. It has to be underlined that studied patients with depression had no other chronic inflammatory processes like chronic heart failure and chronic kidney diseases.

The relationship of TNF-α with the pathogenesis of inflammatory diseases, such as rheumatoid arthritis, psoriasis and heart failure has already been confirmed[4,6]. Depression, in turn, often coexists with chronic inflammatory diseases, such as circulatory failure. The results of the available studies indicate that in the group of patients with depression there is a higher risk of circulatory failure, additionally of a higher degree (according to the NYHA) than in patients without symptoms of depression[7] .

To our knowledge, there are no studies investigating patients with chronic heart failure (CHF) conducting whether the occurrence of certain SNPs of genes encoding TNF-α is associated with the severity of depression. In view of the above, the article attempted to investigate the potential influence of the polymorphism rs1799964 in TNF-α on the survival and clinical outcomes of depression and corresponding circulatory failure.

Patients and Methods

Study Group

66 CHF patients with confirmed diagnosis of depression were enrolled in the study group and followed-up for 72 months (between 2015 and 2021). 37 CHF non-depressed patients were enrolled as control to compare rs1799964 genotype distribution between depressed and non-depressed patients. All CHF patients were treated at the Clinic of Cardiology and Internal Medicine, Department of Cardiology, Military Hospital in Lublin, Poland. European Society of Cardiology guidelines were used for CHF diagnosis and included assessment of echocardiographic assessment (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). The detailed clinical baseline features of the studied depressed CHF patients are summarized in Table I.

For the study protocol, the detailed inclusion (a) diagnosis of depression confirmed by psychiatrist; b) newly diagnosed CHF; c) known medical history and availability of full clinical data; d) signed informed consent to participate in the study) and exclusion (a) condition after the implantation of metallic implants or cardioverter defibrillator; b) acute coronary syndrome or coronary artery bypass grafting within last 6 months; c) hyperthyroidism or hypothyroidism) criteria were applied. Study design was approved by Bioethical Commission in Medical University of Lublin (no of consent: KE-0254/64/2017).

Depression Diagnosis

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

Nutritional Screening

Each CHF patient underwent anthropometric measurements to collect body weight and body mass index (BMI) as well as nutritional screening with the use of subjective global assessment (SGA) and nutritional risk score index (NRS-2002) questionnaires. Fat mass (FM) and fat-free mass (FFM) were derived from bioelectrical impedance analysis (BIA). The repeatable condition of BIA measurements was provided for all patients according to guidelines on reliable impedance measurements. The ImpediMedbioimpedance analysis SFB7 BioImp v1.55 device (Pinkenba,

QLD, Australia) was used to measure above mentioned parameters. Cachexia was diagnosed according to the Evans criteria[8].

Genotyping of rs1799964

Prior to the commencement of the study, 5 mL of peripheral blood were collected from each CHF patient and then stored at −80°C until DNA isolation. DNA was isolated according to manufacturer's protocol of DNA Blood Mini Kit (Quiagen, Canada). The genotyping reaction in Real-Time PCR was performed by StepOnePlus PCR device (Applied Biosystems, Foster City, CA, USA) according to the manufacturer's protocol using Genotyping Master Mix and TaqMan probes specific for rs1799964 (Thermo Fisher Scientific, Waltham, MA, USA). The reaction conditions were introduced based on the manufacturer's protocol. After amplification, the genotypes variants were obtained and analyzed on StepOne Software v2.3 (Applied Biosystems, Foster City, CA, USA).

Statistical Analysis

MedCalc (version 15.3; MedCalc, Belgium) software was applied for statistical purposes. Genotype distribution between depressed and

Table I. Characteristics of the studied group.

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%)

(BMI – body mass index; FM – fat mass. FFM – fat-free mass; CRP – C-reactive group; EF – ejection fraction; LVESD, LVEDD - left ventricular end-diastolic and end-systolic diameters; LAD - left anterior descending artery; TAPSE - tricuspid annular piane systolic excursion; RVOT - right ventricular outflow tract; NYHA – New York Heart Association; SGA – subjective global assessment; NRS – nutritional risk score).

Table II. Distribution of rs1799964 genotypes among CHF patients depending on the depression diagnosis and disease severity.

SNP	Depression (n=66)	Non-depression (n=37)	*p*
CC	10 (15.1%)	4 (10.8%)	
CT	25 (37.9%)	13 (35.1%)	0.734
TT	31 (47%)	20 (54.1%)	
SNP	**Mild depression (n=45; 68.2%)**	**Moderate or severe depression (n=21; 31.8%)**	***p***
CC	7 (15.5%)	3 (14.3%)	
CT	17 (37.8%)	8 (38.1%)	0.990
TT	21 (46.7%)	10 (47.6%)	

non-depressed CHF patients was compared with the use of Chi-square test. Differences in the values of studied parameters between patients bearing various genotypes of rs1799964 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. Cox proportional hazards model was used to investigate association between the overall survival of depressed CHF patients and several variables. Both survival analysis provided hazard ratio (HR) with 95% Confidence Interval (95% CI) calculation. The results demonstrating *p*-values below 0.05 were considered as statistically significant.

Results

Based on the rs1799964 genotyping we recorded the following genotype distribution in the depressed CHF patients: CC in 10 (15.1%) individuals, CT in 25 (37.9%), and TT in 31 patients (47%) (genotypes distribution meet Hardy-Weinberg equilibrium criteria; p=0.202). We also compared the genotype frequency between CHF patients suffering from depression and non-depressed ones. We did not find significant differences concerning genotypes distribution between groups (p=0.734) as well as between individuals with mild and moderate or severe depression (p=0.990) (Table II).

The first objective of the study was to compare clinical, cardiac, laboratory and nutritional measurements between depressed patients depending on the genotype variant of rs1799964. Concerning cardiac parameters EF% was significantly decreased in the CC genotype carriers in contrast to other patients (mean EF%: 36±11 ***vs*** 44±14 and 46±7; p=0.023). Moreover, the stages III and IV of the NYHA were more frequently recorded in CC patients than others (frequency of NYHA III and IV: 80% ***vs*** 36% and 35.5%; p=0.033). Regarding laboratory parameters, we noticed the significant increase in serum inflammatory markers (CRP and TNF-α) in CC individuals (mean CRP concentration: 35.9±14.7 mg/L for CC, 14.2±17.6 mg/L for CT and 10.51±14.2 mg/L for TT; p=0.003 and mean TNF-α concentration: 6.82±1.09 pg/mL for CC, 4.45±1.40 pg/mL for CT and 3.86±1.20 pg/mL for TT; p<0.001). Additionally, CC genotype carriers demonstrated significantly decreased level of hemoglobin (mean hemoglobin level: 11.9±1.0 g/dL ***vs.*** 13.4±1.7 g/dL and 13.2±1.4 g/dL; p=0.029) and serum albumin (mean albumin concentration: 2.91±0.76 g/dL ***vs.*** 3.67±0.44 g/dL and 3.55±0.53 g/dL; p=0.007). Compared with T allele carriers, the CHF patients bearing CC genotype were more frequently diagnosed as cachectic (cachexia incidence for CC – 80% ***vs*** 28% for CT and 38.7% for TT; p=0.017). Differences in the values of clinical, cardiac and nutritional measurements among CHF patients with various genotype of TNF-α rs1799964 is presented in Table III.

The subsequent goal of the study was to assess factors affecting overall 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, 80% in CC group, 60% in CT and 48.4% in TT group. Independent unfavorable factors affecting survival in the studied patients were as follows: NYHA grade III or IV (HR=2.38; p=0.011), CC genotype of rs1799964 (HR=3.88; p=0.009 for CC ***vs.***CT ***vs.*** TT and HR=3.11; p=0.004 for CC ***vs.*** CT+TT), hemoglobin concentration below 12 g/dL (HR=2.21; p=0.021) and CRP level over 3 mg/L (HR=2.06; p=0.030) (Table IV).

Survival probability demonstrated by Kaplan-

Table III. Differences in the values of clinical, cardiac and nutritional measurements among CHF patients with various genotype of TNF-α.

Factor		CC (n=10; 15.1%)	CT (n=25; 37.9%)	TT (n=31; 47%)	p
Age±SD (years)		75±13	72±17	73±11	0.902
Gender	Male	6 (60%)	13 (52%)	17 (54.8%)	0.911
	Female	4 (40%)	12 (48%)	14 (45.2%)	
Systolic blood pressure (mmHg)		124±15	136±22	130±25	0.426
Diastolic blood pressure (mmHg)		74±9	78±16	74±13	0.548
EF%		36±11[a]	44±14[b]	46±7[b]	0.023
NT-proBNP (pg/mL)		5106±3900	3148±2907	3890±2289	0.627
LVESD (cm)		3.9±0.8	4.1±0.9	4.3±1.0	0.556
LVEDD (cm)		4.9±1.2	5.1±0.9	5.3±1.1	0.599
LAD (cm)		4.4±0.6	4.4±0.6	4.5±0.7	0.645
RVOT (cm)		3.6±0.5	3.5±0.6	3.4±0.4	0.741
TAPSE (cm)		1.7±0.4	1.9±0.3	1.8±0.5	0.446
PASP (mmHg)		42±15	41±15	42±14	0.935
NYHA	I	1 (10%)	6 (24%)	7 (22.6%)	0.148
	II	1 (10%)	9 (36%)	10 (32.2%)	
	III	2 (20%)	7 (28%)	7 (22.6%)	
	IV	6 (60%)	3 (12%)	7 (22.6%)	
	I and II	2 (20%)	16 (64%)	20 (64.5%)	0.033
	III and IV	8 (80%)	9 (36%)	11 (35.5%)	
Diabetes mellitus	Yes	5 (50%)	7 (28%)	14 (45.2%)	0.323
	No	5 (50%)	18 (72%)	17 (54.8%)	
Renal failure	Yes	3 (30%)	6 (24%)	10 (32.3%)	0.791
	No	7 (70%)	19 (76%)	21 (67.7%)	
Smoking status	Smoker	5 (50%)	11 (44%)	22 (71%)	0.111
	Non-smoker	5 (50%)	14 (56%)	9 (29%)	
Weight (kg)		79±13	86±20	85±12	0.120
BMI (kg/m2)		27.51±4.76	27.78±4.73	30.76±8.15	0.212
FM (kg)		22.6±14.4	24.7±12.0	26.8±13.2	0.770
FFM (kg)		52.9±16.9	54.2±12.6	55.7±17.7	0.892
Albumin (g/dL)		2.91±0.76[a]	3.67±0.44[b]	3.55±0.53[b]	0.007
Triglycerides (mg/dL)		100±41	105±54	104±64	0.971
Total cholesterol (mg/dL)		139±28	167±46	164±43	0.318
Creatinine (mg/dL)		1.46±0.50	1.21±0.43	1.26±0.41	0.579
Hemoglobin (g/dL)		11.9±1.0[a]	13.4±1.7[b]	13.2±1.4[b]	0.029
CRP (mg/L)		35.9±14.7[a]	14.20±17.6[b]	10.51±14.2[b]	0.003
TNF-α (pg/mL)		6.82±1.09[a]	4.45±1.40[b]	3.86±1.20[b]	<0.001
Cachexia	Yes	8 (80%)	7 (28%)	12 (38.7%)	0.017
	No	2 (20%)	18 (72%)	19 (61.3%)	
NRS	<3	4 (40%)	18 (72%)	19 (61.3%)	0.210
	≥3	6 (60%)	7 (28%)	12 (38.7%)	
SGA	A	3 (30%)	13 (52%)	16 (51.6%)	0.070
	B	2 (20%)	10 (40%)	10 (32.3%)	
	C	5 (50%)	2 (8%)	5 (16.1%)	
	A	3 (30%)	15 (60%)	16 (51.6%)	0.276
	B or C	7 (70%)	10 (40%)	15 (48.4%)	

(BMI – body mass index; FM – fat mass. FFM – fat-free mass; CRP – C-reactive group; EF – ejection fraction; LVESD, LVEDD - left ventricular end-diastolic and end-systolic diameters; LAD - left anterior descending artery; TAPSE - tricuspid annular piane systolic excursion; RVOT - right ventricular outflow tract; NYHA – New York Heart Association; SGA – subjective global assessment; NRS – nutritional risk score)

Meier estimator graph his presented in Fgure 1A and 1B.

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: LVESD >4.0 cm (HR=11.2; $p<0.001$), CC genotype of rs1799964 (HR=8.87; $p<0.001$), LAD >4.0 cm (HR=3.98; $p=0.008$) and NYHA grade III or IV (HR=3.45;$p=0.003$) (Table V).

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

	Log-rank test (univariate analysis)		
Factor	**Median OS (favorable vs unfavorable)**	**HR [95%CI]**	***p***
NYHA III or IV	65 *vs* 56 months	2.38 [1.221-4.633]	0.011
CC genotype of TNF-α	69 vs 60 *vs* 20 months	3.88 [0.972-15.075]	0.009
CC genotype of TNF-α	67 *vs* 20 months	3.11 [0.878-10.93]	0.004
Hemoglobin <12 g/dL	68 *vs* 60 months	2.21 [0.951-5.148]	0.021
CRP >3 mg/L	72 *vs* 56 months	2.06 [0.951-4.439]	0.030

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

Covariate	**HR [95%CI]**	***p***
LVESD >4.0 cm	11.2 [2.95-50.271]	<0.001
CC genotype of TNF-α	8.87 [3.452-28.792]	<0.001
LAD > 4.0 cm	3.98 [1.451-10.869]	0.008
NYHA III or IV	3.45 [1.512-7.826]	0.003

Discussion

At present, gene polymorphisms and their role in the development, course and therapy of depression are currently in the spectrum of interest of scientists. Particular attention is paid to polymorphisms in genes encoding cytokine mediating the development of inflammation, i.e., IL-1, IL-6 or TNF-α, which seem to be also crucial for the depressive disorders, but also for chronic diseases, that often coexist with depression. High levels of inflammatory markers have been repeatedly observed and described in the course of depression, especially IL-6 and CRP[5,9]. Depression often coexists with circulatory failure, and the results of available studies indicate, that in the group of patients with depression there exists a higher risk of circulatory failure and its more severe course (according to the NYHA) than in patients without depression[7]. In the light of the recent studies, circulatory failure is related to the rs1799964 polymorphism, and such a predisposition to coronary heart disease, and thus the subsequent development of heart failure, has already been described. rs1799964 in the TNF-α seems to be related to coronary artery disease, which is proved by the results of a few studies[10]. The severity of depression and its association with coronary artery disease have been analyzed so far and confirmed by clinical trials[11].

The relationship between TNF-α and the pathogenesis of inflammatory diseases, such as rheumatoid arthritis, psoriasis and heart failure has also been confirmed, which made it possible to introduce TNF-α brokers in the treatment of these diseases[6]. While TNF blockers are used in the treatment of psoriasis, the data for the treatment of heart failure in the course of rheumatoid arthritis seem no longer conclusive. The clinical effect is not fully achieved, and the potential benefits appeared only with combined treatment: TNF blocker and another anti-inflammatory drug[12,13] . According to Sarzi-Puttini et al[13], the cause of therapy failure may be attributed to various TNF-α variants, which leads to the production of variable cytokine levels and the associated severity of inflammation. According to the authors, therapy with TNF blockers may be acceptable only with appropriate monitoring and only in stable heart failure with the severity of NYHA I / II, while for patients with stage - NYHA III / IV, it is forbidden[11,13]. In the light of the obtained results, this thesis begins to have some justification. In patients with TT rs1799964 genotype, failure was diagnosed more often at NYHA I / II level than with CT and CC genotypes (p=0.033), while failure at NYHA III / IV level - most often diagnosed with CC genotype (p=0.033). However, no differences were noted between the distribution of *TNF*-α genotypes and the incidence or severity of depression.

In the studied group of patients, the level of TNF-α was definitely the highest in CC homozygotes, and the lowest in patients with the TT geno-

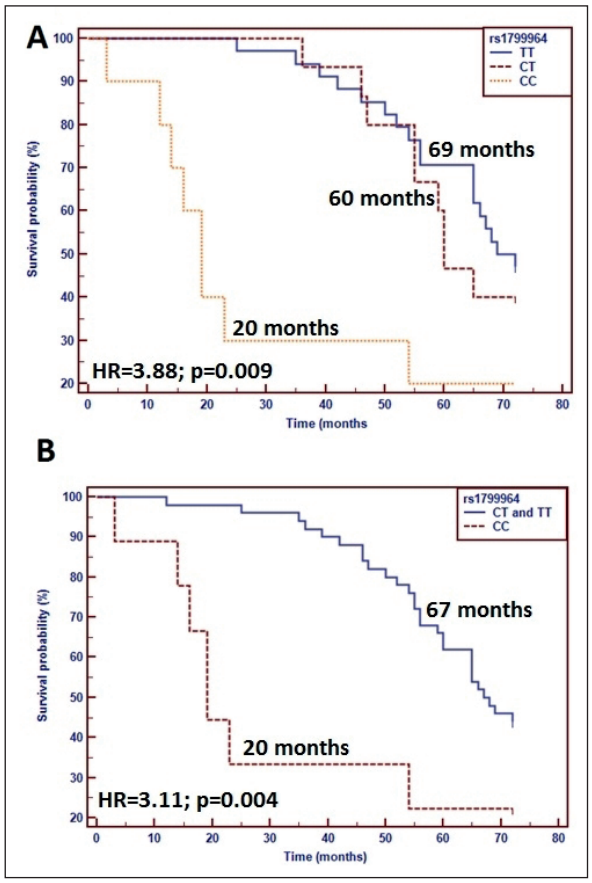

Figure 1. Impact of the rs1799964 genotypes on overall survival of depressed CHF patients. ***A***, Survival curves for CC, CT and TT genotype carriers. ***B***, Survival curves for CC and CT+TT genotypes.

type (6.82 ± 1.09 pg / mL *vs.* 3.86 ± 1.20 pg / mL; $p<0.001$). There was also an adverse effect of the CC genotype on the life expectancy of patients with CHF and depression. Based on the results, the CC genotype can be considered as an unfavorable prognostic factor (median survival: 67 months for TT and T *vs.* 20 months for CC; HR = 3.11, $p=0.004$). Among the tested cytokines, the level of TNF-α in patients with depression is described in many publications as higher than in the control group[14]. The above results seem to confirm the potential influence of rs1799964 TNF-α as well as TNF-α itself on the clinical shape of both depression and heart failure. The severity of inflammation in patients with the CC genotype was also reflected in the level of circulating CRP, the concentration of which was higher in the aforementioned group of depressed patients (mean CRP concentration: 35.9±14.7 mg/L *vs.* CT: 14.20±17.6 mg/L and TT: 10.51±14.2 mg/L; $p=0.003$).

In the group of patients diagnosed with depression, the higher severity of depression (according to the BDI scale) is related to the lower EF%, which translated into a reduction in the quality of life of patients[15]. In depressed patients with CC genotype, significantly lower EF% was noted than in TT and CT carriers (mean EF%: 36 ± 11 *vs.* 46 ± 7 and 44 ± 14; $p=0.023$). Moreover, a decreased level of hemoglobin was noted in somatically unburdened patients with depression[16]. Other studies have shown that in cancer patients, the lower the hemoglobin level, the higher the risk of depression[17,18]. In the studied group of patients, a significantly lower level of hemoglobin was recorded in patients with the CC genotype (mean: 11.9±1.0 g/dL *vs.* 13.4±1.7 and 13.2±1.4 g/dL; $p=0.029$), which explains the greater severity of inflammation in this group of individuals.

In patients with diagnosed depression, we will probably find a higher susceptibility to the development of cachexia, in the literature we may 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 was performed on a group of patients with simultaneous oncological diagnosis[19]. Patients with the CC genotype had a greater percentage of cachectic patients than those with other genotypes (CC: 80% *vs.* CT: 28% and TT: 38.7%; $p=0.017$). This is probably associated with the development of more severe inflammation in carriers of the CC genotype and a higher predisposition to develop cachexia.

In this paper, no correlation was found between rs1799964 and the occurrence of depression and its severity, while the studied polymorphism seems to have a significant impact on the course of the underlying disease accompanied by depression. The presence of the CC genotype in patients with depression and CHF can be considered as an unfavorable prognostic factor related to the high risk of shortening survival, which is reflected in the severity of inflammation, the percentage of cachectic patients and deterioration in cardiac parameters.

Conclusions

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.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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