JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Original Article DOI: https://doi.org/10.23950/jcmk/12252

Prognostic value of depression, anxiety disorders and inflammatory markers in patients with reduced and mildly reduced ejection fraction heart failure

Emine Gazi[1], Elif Karaahmet[2], Hakan Türkön[3], Ahmet Barutçu[1], Uğur Küçük[1]

[1]Department of Cardiology, Faculty of Medicine, Çanakkale Onsekiz Mart University, Çanakkale, Turkey
[2] Department of Psychiatry, Sağlık Bilimleri University, Okmeydanı Research and Education Hospital, İstanbul, Turkey
[3] Department of Biochemistry, Meddem Hospital, Isparta, Turkey

Received: 2022-05-10.
Accepted: 2022-06-09

J Clin Med Kaz 2022; 19(4):4-12

Corresponding author:
Uğur Küçük.
E-mail: drugurkucuk@hotmail.com;
ORCID: 0000-0003-4669-7387

Abstract

Aim: Patients with heart failure (HF) have greater rates of depression and anxiety than the general public. The researchers wanted to investigate if there was a relationship between depression, anxiety, and inflammatory markers, as well as survival and hospitalization, in HF patients with reduced and mildly reduced ejection fractions (HFrEF and HFmrEF).

Materials and methods: This prospective research comprised 122 consecutive individuals having a left ventricular ejection fraction (LVEF) of less than 50%. The inflammatory system was investigated using the specific markers. Hamilton Depression and Anxiety Rating Scales (HAM-D and HAM-A) were used to diagnose of depression and anxiety.

Results: The median duration of follow-up was 36.4 months. Non-survivors had lower glomerular filtration rate, LVEF, and blood sodium levels than survivors, while they were older. Age, LVEF, and GFR are independent predictors for mortality. No independent relation was found between depression, anxiety, inflammatory parameters and mortality. Anxiety was found as independent predictors for hospitalization.

Conclusion: Anxiety, depression, and inflammatory conditions indicators were not associated with mortality in people with HFrEF and HFmrEF. Neutrophil-to-lymphocyte ratio (NLR) and anxiety were found as independent predictors for hospitalization.

Key words: heart failure, depression, anxiety, inflammatory markers, mortality

Introduction

Heart failure (HF) still reduces the quality of life because of recurrent hospitalizations, and it has high mortality despite improvements in medical and interventional treatment strategies. HF was reported to be related to psychological stress and incidence of clinically significant anxiety disorders (8%–16%), including general anxiety disorder and panic attack [1,2]. The relationship between HF and depression is a new area in daily practice. The frequency of depression in patients with HF is 2–3 times higher than that in the normal population [3]. Sometimes, depression is overlooked in routine daily practice because these two diseases have many similar symptoms, and HF symptoms may lead to over-reporting in patients with depression who are thought to have worsened perception [4].

Like HF, depression is associated with high morbidity and mortality rates [5]. While some investigations have reported that the concurrence of two disorders has increasing adverse outcomes, others reported the opposite. The mechanism of the relationship between depression with HF progression and mortality is unclear. Inflammation is thought to be a possible mechanism in patients with these conditions [6-9]. High levels of inflammatory markers may be related to the progression of HF [10]. Some studies have supposed that in patients with depression without HF, inflammatory markers are also increased [11,12]. However, it is unknown whether inflammation is the cause or consequence.

Our study aimed to explore the relationship among inflammatory markers, anxiety, and depression and determine the prognostic effects on long-term

mortality, hospitalization, and quality of life in patients having HF with reduced and mildly reduced ejection fraction (HFrEF and HFmrEF) by using objective psychiatric evaluation.

Materials and methods

Study population

Consecutive outpatients with HF visiting the cardiology clinic between November 2011 and September 2013 were included. Patients with HF and left ventricular ejection fraction (LVEF) ≤50%, aged <75 years, and were stable for at least one-month. Patients with malignancy, liver failure, chronic inflammatory disease, and cognitive disorders, aged <18 years and >75 years (quality of life may affect test results in the older population), were excluded. All patients have received appropriate treatment for HF with reduced ejection fraction and other comorbidities.

Of the 160 patients, 131 agreed to participate. 9 individuals were excluded because they did not have a depression score at the time of inclusion and blood was not taken at the time of baseline. Therefore, 122 patients who had complete data at inclusion (blood and questionnaires) were included. Routine controls were performed every 6 months. In this study, the follow-up was completed in December 2015. An interview was used to examine demographic and clinical variables. New York Heart Association (NYHA) functional class information, risk factors, comorbidities, and medication was obtained from the patients through interview by a cardiologist.

Blood sample

Venous blood sample was obtained with a jelly tube at admission. Samples were centrifuged at 4000 rpm. Serum samples were stored −80°C for analysis of B-type natriuretic peptide (BNP), IL-6, tumor necrosis factor (TNF)-α, and high-sensitivity CRP (hs-CRP). IL-6 (Catalog No. KHC0061, Invitrogen Corporation, Camarillo, CA, USA) and TNF-α (Catalog No.: KHC3011, Invitrogen Corporation) levels were studied by enzyme-linked immunosorbent assay (ELISA) in ELX 808 IU model ELISA device. The NT-proBNP level was studied by using the electrochemiluminescence method in Cobas e601 analyzer. The hs-CRP level was examined by the immunoturbidimetric method in Cobas c501 analyzer by using Roche kits (Roche Diagnostics GmbH). All routine biochemical tests were carried out with the Cobas 6000 Integra (Roche) auto-analyzer using the chemiluminescence method at admission. Transthoracic echocardiography was performed on each patient in the outpatient clinic. Simpson's method was used to assess the LVEF.

An independent psychiatrist evaluated patients. The Hamilton Depression Rating Scale for depression (HAM-D), HAM scale for anxiety (HAM-A), and Short-Form 36 (SF-36) quality of life scale were used in the face-to-face interview. HAM-D score >7 indicates depression [13]. HAM-A, which is a standard psychiatric interview commonly used in research and clinical trials, score >11 represents anxiety [14]. The SF-36, which is a self-questionnaire survey, was used to determine the patients' quality of life. Physical health composite score (PCS) and mental health composite score were calculated as follows:

SF-36PCS= Σ (z score of each scale x respective physical factor coefficient) x 10 + 50

SF-36 MCS = Σ (z score of each scale x respective mental factor coefficient) x 10 + 50 formulas in the SPSS software [15].

After the initial assessment, all patients were periodically referred to our hospital for control checkup. Patients were interviewed (directly or over the phone) to acquire endpoint information, their families, hospital records, or social insurance if patient information cannot be reached.

Depression and anxiety were only assessed at baseline. Cardiovascular death was described as the primary endpoint, and the secondary endpoint was defined as hospitalization because of cardiovascular disease.

All participants agreed and provided consent to participate in the research, and the approval of the local ethics committee was obtained (Date: 09/03/2012, Decision no: 050.99-55). The study follows the principles guided in the Helsinki Declaration.

Statistical analysis

All statistical analyses were carried out with the SPSS program (version 21.0, SPSS, Chicago, IL, USA). Quantitative/continuous variables with a skewed distribution were summarized as median and interquartile range, continuous variables with a normal distribution were summarized as mean and standard deviation, and Percentages were used to express qualitative characteristics (%). To determine the normality of all measures, the Kolmogorov–Smirnov test was used. The Student T or Mann–Whitney U-test was used to compare continuous variables between the two groups. The Chi-square test was used to compare categorical variables. Correlations between LVEF, BNP, IL-6, hs-CRP, BNP, HAM-A score, HAM-D score, and SF-36 score were evaluated by a Pearson correlation test. A Kaplan–Meier with the log-rank statistics was used to determine survival rates for depression and anxiety. Cox proportional regression analysis including age, LVEF, GFR, serum sodium level, NLR, inflammatory markers, HAM-A, HAM-D scores and SF-36 parameters was as independent predictors of mortality. A p value <0.05 was accepted significantly.

Results

Baseline demographic and clinical parameters of the study population are summarized in Table 1. Most of the patients were male (77.9%) and hypertensive (69.7%), and 27.9% of the population has atrial fibrillation. Patients were receiving appropriate medications, including renin–angiotensin–aldosterone system blockers and beta-blockers. Moreover, 4.9% and 19.7% of the patients have mild and severe depression according to the HAM-D scale, respectively, and 19.7% and 36.9% of the patients have mild and severe anxiety according to the HAM-A scale, respectively. A total of 39 (32%) patients died; 45 (36.9%) patients were hospitalized at a median follow-up period of 36.4 months.

Depression and anxiety

Results of the comparison of depression and anxiety groups are summarized in Table 2. Baseline demographic parameters, endpoints, and inflammatory marker levels were similar in patients with and without depression except for the use of beta-blockers (91.1% vs. 76.6%, p=0.045). HAM-D and HAM-A scale scores were significantly high, and the SF-36 scores were significantly low in patients with both depression and anxiety. Baseline demographic, laboratory, and inflammatory marker findings were similar in patients with and without anxiety and depression. Patients with anxiety had a greater hospitalization rate (44.9% vs. 26.4%, p=0.036).

Table 1 Demographic, laboratory and psychological parameters of study population

Parameter	Value
Age (Years)	63.5 ± 9.8
Male/Female	95/27
Heart Rate (bpm)	76 ± 12
Ejection Fraction (%)	34.3±6.6
BMI (kg/m2)	28.3 ± 5.2
Hypertension % (n)	%69.7 (85)
Diabetes Mellitus % (n)	%41 (50)
CAD history % (n)	64.8 % (79)
Smoking % (n)	19.7 % (24)
Atrial Fibrillation % (n)	27.9 % (34)
Medications % (n)	
ACE inhibitor	61.5 % (75)
Beta Blocker	82 % (100)
ARB	20.5 % (25)
Hydrochlorothiazide	43.4% (53)
Furosemide	48.4 % (59)
MRA	46.7 % (57)
Oral anticoagulation	22.9 % (28)
Laboratory analysis	
Glucose (mg/dl)	136.9 ± 7.7
TG (mg/dl)	141.5 ± 76.2
LDL (mg/dl)	113.7 ± 3.1
HDL (mg/dl)	44.9 ± 12.7
GFR	60.9±20.4
NLR	3.19±1.77
SF physiological function	16.8 ± 10.5
SF physiological role	15.9 ± 8.7
SF pain	28.2 ± 11
SF general health	26.9 ±10.6
SF vital	33.8 ± 13
SF social function	37 ± 13.9
SF mental health	42.1 ± 28.6
HAM-D	6 (1-43)
HAM-D (8-16)	4.9 % (6)
HAM-D (>16)	27 % (33)
HAM-A	14 % (1-40)
HAM-A (11-17)	19.7 % (24)
HAM-A (>17)	36.9 % (45)
Follow-up	
Time (month)	36.4 (1-41)
Death % (n)	32 % (39)
Hospitalisation % (n)	36.9 (45)
Death ± Hospitalisation % (n)	54.1 % (66)

BMI: Body Mass Index, CAD: Coronary Artery Disease, ACE: Angiotensin Converting Enzyme, ARB: Angiotensin Receptor Blocker, MRA: Mineralocorticoid receptor antagonist, TG: Triglyceride, LDL: Low Density Lipoprotein, HDL: High Density Lipoprotein, GFR: Glomerular Filtration Rate, NLR: Neutrophile to Lymphocyte Ratio, SF: Short Form for quality of life, HAM-D: Hamilton D rating scale, HAM-A: Hamilton A rating scale.

Mortality groups

When compared with survivors, non-survivors patients were older (68.6±9.7 vs. 61 ± 8.8 years, p < 0.001) and have lower LVEF (32.5±6.4% vs. 35.1±6.5%, p=0.037), decreased glomerular filtration rate (GFR) (51.3±19.5 vs. 65.6±19.3 ml/min, p<0.001), and blood sodium level (135±19 vs. 139±2 mEq/ml, p=0.04). NYHA functional capacity was poor in non-survivors (p<0.001) (Table 3).

Survival analysis

Kaplan–Meier survival curves of depression and anxiety are shown in Figure 1 and 2. Univariate Cox regression analysis showed that age, LVEF, GFR, serum sodium level, neutrophil-to-lymphocyte ratio (NLR), SF-36 pain, SF-36 general health, and NYHA functional classifications were predictors of mortality. Age, LVEF, and GFR were independent predictors of mortality (Table 4).

Figure 1 - Kaplan–Meier survival curves of the study population according to depression groups.

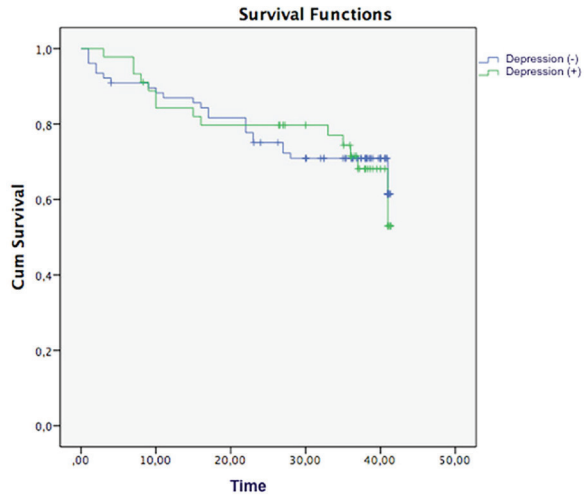

Figure 2 - KaplaMeier survival curves of the study population according to anxiety groups.

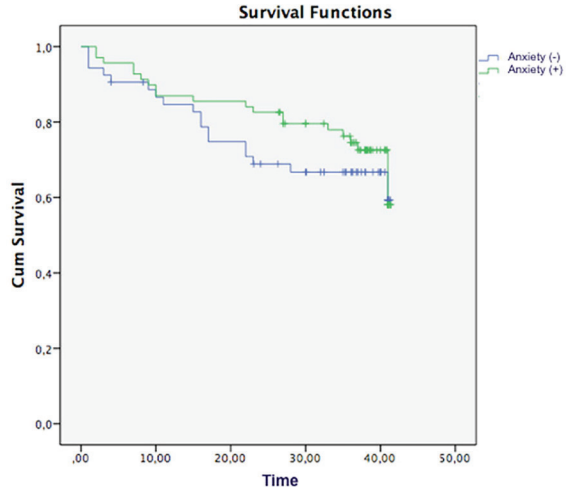

Figure 3 - Kaplan–Meier survival curve according to the effective cut-off value of the neutrophil-to-lymphocyte ratio

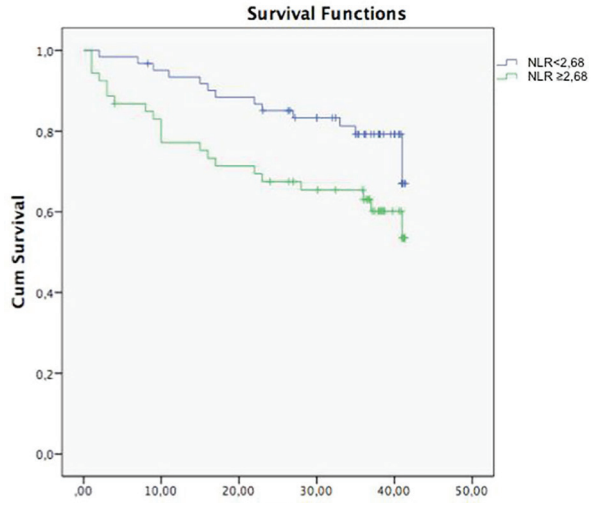

Table 2 Comparisons of demographic, laboratory and psychological parameters of study groups

Parameter	Depression (+) n (45)	Depression (-) n (77)	p	Anxiety (+) n (68)	Anxiety (-) n (54)	p
Age (Years)	64.0 ± 9.5	63.1 ± 9.9	0.685	63.0 ± 9.6	64.0 ± 9.9	0.593
Male, % (n)	82.2 % (37)	75.3 % (58)	0.376	76.8 (53)	79.2 (42)	0.748
Heart Rate (bpm)	76±12	76 ± 12	0.910	75 ± 11	78 ± 14	0.509
Ejection Fraction (%)	33.6 ± 7.3	34.7 ± 6.1	0.369	34.7 ± 6.7	33.7 ± 6.4	0.435
BMI (kg/m2)	28.3 ± 5.5	28.3 ± 5.1	0.990	28.4 ± 5.5	28.2 ± 5	0.851
Hypertension % (n)	68.9 (31)	71.1 (54)	0.801	69.1 (47)	71.7 (38)	0.738
Diabetes Mellitus % (n)	37.8 (17)	43.4 (33)	0.542	39.7 (27)	43.4 (23)	0.683
CAD history % (n)	66.7 (30)	63.6 (49)	0.735	63.8 (44)	66 (35)	0.795
Smoking % (n)	20 (9)	19.7 (15)	0.761	19.1 (13)	20.8 (11)	0.775
Atrial Fibrillation % (n)	38.5 (15)	28.4 (19)	0.213	66.4 (18)	48.4 (16)	0.647
Medications % (n)						
ACE inhibitor	644 (29)	59.7 (46)	0.606	62.3 (43)	60.4 (32)	0.827
Beta Blocker	91.1 (41)	76.6 (59)	**0.045**	87 (60)	75.5 (40)	0.102
ARB	22.2 (10)	19.5 (15)	0.717	18.8 (13)	22.6 (12)	0.606
ASA	88.9 (40)	76.6 (59)	0.095	85.5 (59)	75.5 (40)	0.160
Hydrochlorothiazide	48.9 (22)	40.3 (31)	0.354	478 (33)	37.7 (20)	0.265
Furosemide	51.1 (23)	46.8 (36)	0.642	49.3 (34)	47.2 (25)	0.818
Laboratory analysis						
Glucose (mg/dl)	109 (73-394)	112 (72-315)	0.716	111 (73-394)	112 (72-315)	0.822
TG (mg/dl)	140 ± 74	142 ± 77	0.895	146 ± 80	135 ± 70	0.463
LDL (mg/dl)	112 ± 29	114 ± 38	0.752	113 ± 33	113 ± 37	0.952
HDL (mg/dl)	41 ± 10	47 ± 13	**0.039**	43 ± 11	46 ± 13	0.236
GFR	60.4 ± 18.2	61.2 ± 21.7	0.840	62.9 ± 20	58.4 ± 20.6	0.234
NLR	3.49±1.86	3.02±1.7	0.181	3.31±1.78	3.05±1.75	0.430
Hs-CRP	3.7 (0.3-69)	43 (0.4-38)	0.493	4.1 (0.3-69)	4.4 (0.7-18.1)	0.936
TNFα	17.3 (6.6-243.1)	16.7 (2.9-237.4)	0.937	17.3 (2.9-243.1)	16.2 (5.4-139.8)	0.960
IL-6	5.6 (1.9-209.9)	5.8 (2.2-452.9)	0.375	5.3 (2.5-209.9)	6.9 (1.9-452.9)	0.064
NT-proBNP	923 (43-13179)	1134(105-134)	0.306	923(43-13179)	1257 (105-35000)	0.106
Depression and anxiety						
SF physiological function	11 ± 6	20 ± 11	**0.000**	12 ± 6	23 ± 11	**0.000**
SF physiological role	10 ± 5	19 ± 8	**0.000**	12 ± 6	20 ± 8	**0.000**
SF pain	22 ± 8	31 ± 11	**0.000**	24 ± 9	32 ±11	**0.000**
SF general health	21 ± 7	30 ± 10	**0.000**	23 ± 9	31 ± 10	**0.000**
SF vital	23 ± 6	40 ± 11	**0.000**	28 ± 11	40 ± 11	**0.000**
SF social function	24 ± 8	44 ± 11	**0.000**	31 ± 14	43 ± 10	**0.000**
SF mental health	23 ± 11	53 ± 30	**0.000**	32 ± 17	54 ± 35	**0.000**
HAM-D	21 (7-43)	4 (1-7)	**0.000**	13 (1-43)	4 (1-24)	**0.000**
HAM-A	22 (3-43)	8 (1-43)	**0.000**	22 (11-43)	5 (1-10)	**0.000**
Baseline NYHA Class			0.420			0.427
I	8.9 (4)	5.2 (4)		8.7 (6)	3.8 (2)	
II	71.1 (32)	62.3 (48)		66.7 (46)	64.2 (34)	
III	20 (9)	31.2 (24)		24.6 (17)	30.2 (16)	
Follow-up						
Time (month)	36.5 (3-41)	36.3 (1-41)	0.934	37 (2-41)	35 (1-41)	0.062
Death % (n)	33.3 (15)	31.2 (24)	0.805	30.4 (21)	34 (18)	0.679
Hospitalisation % (n)	44.4 (20)	32.5 (25)	0.186	44.9 (31)	26.4 (14)	**0.036**

BMI: Body Mass Index, CAD: Coronary Artery Disease, ACE: Angiotensin Converting Enzyme, ARB: Angiotensin Receptor Blocker, TG: Triglyceride, LDL: Low Density Lipoprotein, HDL: High Density Lipoprotein, GFR: Glomerular Filtration Rate, hs-CRP: High sensitive C-reactive protein, TNFα: Tumor necrosis factor alfa, IL-6: Interleukin-6, NT-proBNP: N-terminal pro-brain natriuretic peptide, NYHA: New York Heart Association, SF: Short Form for quality of life, HAM-D: Hamilton D rating scale, HAM-A: Hamilton A rating scale.

A receiver operating characteristics curve analysis was performed for NLR. The area under the curve was 0.62 (CI 0.50–0.73, p=0.042), and 2.68 was selected as an optimal effective cut-off point according to sensitivity of 60% and specificity of 60%). Kaplan–Meier's survival curve of NLR is shown in Figure 3.

Hospitalization

Age, LVEF, serum sodium level, SF-36 pain, MCS, NLR, HAM-D score, HAM-A score, and NYHA functional capacity were found as predictors in the univariate analysis. NLR, HAM-A score, serum sodium level, and NYHA functional capacity were found as independent predictors for hospitalization (Table 5).

Table 3 Comparisons of survivors and non-survivors

Parameter	Non-Survivors n (39)	Survivors n (83)	p
Age (Years)	68.6 ± 9.7	61±8.8	**0.000**
Male	79.5 (31)	77.1 (64)	0.768
Ejection Fraction (%)	32.5 ± 6.4	35.1 ± 6.5	**0.037**
BMI (kg/m2)	27.6 ± 5.4	28.6 ± 5.2	0.398
Hypertension % (n)	76.9 (30)	67.1 (55)	0.268
Diabetes Mellitus % (n)	46.2 (18)	39 (32)	0.457
CAD history % (n)	59 (23)	67.5 (56)	0.360
Smoking % (n)	35.8 (14)	36.1 (30)	0.569
Atrial Fibrillation % (n)	39.4 (13)	28.8 (21)	0.462
Medications % (n)			
ACE inhibitor	56.4 (22)	63.9 (53)	0.431
Beta Blocker	76.9 (30)	84.3 (70)	0.321
ARB	28.2 (11)	16.9 (14)	0.148
ASA	71.8 (28)	85.5 (71)	0.07
Hydrochlorothiazide	46.2 (18)	42.2 (35)	0.679
Furosemide	51.3 (20)	47 (39)	0.658
MRA	43.6 (17)	45.8 (38)	0.820
Laboratory analysis			
Glucose (mg/dl)			0.259
TG (mg/dl)	136 ± 72	143 ± 78	0.692
LDL (mg/dl)	116 ± 37	112 ± 34	0.544
HDL (mg/dl)	41 ± 10	46 ± 13	0.116
GFR	51.3 ± 19.5	65.6 ± 19.3	**0.000**
Sodium	135 ± 19	139 ± 2	**0.04**
Potassium	4.8 ± 1.1	4.6 ± 0.4	0.131
NLR	3.8 ±2.8	2.8 ± 1.3	**0.005**
hsCRP	6.4 (0.3-39.8)	4 (2.9-16.2)	0.120
TNF alfa	17.5 (8.3-17.5)	16.2 (2.9-243.1)	0.190
IL-6	6.8 (3.6-367.8)	5.6 (1.9-452.9)	0.290
NT-proBNP	1257 (223-7392)	961 (43-35000)	0.199
Depression and anxiety			
SF physiological function	15 ± 9	17 ± 11	0.354
SF physiological rol	13 ± 7	16 ± 9	0.081
SF pain	23 ± 9	30 ± 11	**0.003**
SF general health	23 ± 8	28 ± 11	**0.014**
SF vital	33 ± 13	34 ± 13	0.637
SF social function	34 ± 13	38 ± 13	0.123
SF mental health	45 ± 43	40 ± 17	0.435
HAM-D	5 (1-43)	6 (1-38)	0.858
HAM-A	11 (3-43)	13 (1-43)	0.456
NYHA Class			**0.000**
I	7.7 (3)	6 (5)	
II	41 (16)	77.1 (64)	
III	48.7 (19)	16.9 (14)	
Follow-up Time	16 (1-41)	38 (4-41)	**0.000**

BMI: Body Mass Index, CAD: Coronary artery disease, ACE: Angiotensin Converting Enzyme, ARB: Angiotensin Receptor Blocker, TG: Triglyceride, LDL: Low Density Lipoprotein, HDL: High Density Lipoprotein, GFR: Glomerular Filtration Rate, NLR: Neytrophile to Lymphocyte ratio, hs-CRP: High sensitive C-reactive protein, TNFα: Tumor necrosis factor alfa, IL-6: Interleukin-6, NT-proBNP: N-terminal pro-brain natriuretic peptide, NYHA: New York Heart Association, HAM-D: Hamilton D rating scale, HAM-A: Hamilton A rating scale.

Correlation analysis

A Pearson correlation analysis showed that NLR was negatively correlated with LVEF (r= −0.218, p=0.002) and hs-CRP and IL-6 levels were positively correlated with NT-proBNP (r=0.368, p<0.001 and r=0.650, p<0.001, respectively). Table 6 shows other correlated parameters.

Discussion

In our study including HFrEF and HFmrEF patients we found that 1) Depression and anxiety were not related to mortality 2) NLR, NYHA, and HAM-A scores were independent predictors for hospitalization 3) Age, LVEF, and GFR were independent predictors of mortality 4) Serum NT-proBNP, IL-6, TNF-α, and hs-CRP levels were not related to mortality, also.

The incidence of depression is nearly 2–3 times increased in patients with HF than in the normal population, and the estimated prevalence is 24%–42% [16]. The prevalence of depression in HF differs by health status, demographic factors, and social factors. In our study population, depression and anxiety occurred in 36.9% and 56.6% of the cases, respectively, similar to that in previous studies. Depression has also been associated with developing HF [17]. Because arguments on

Table 4 Cox regression analysis for cardiovascular mortality

	Univariate			Multivariate		
Variable	**HR**	**CI 95%**	**p**	**HR**	**CI 95%**	**p**
Age (years)	1.08	1.04-1.12	**<0.001**	1.08	1.04-1.14	**<0.001**
EF	0.94	0.9- 0.98	**0.015**	0.93	0.89-0.98	**0.014**
GFR	0.96	0.95-0.98	**<0.001**	0.97	0.95-0.99	**0.028**
Sodium	0.98	0.96-0.99	**0.036**			
NLR	1.31	1.12-1.52	**<0.001**			
hsCRP	1.01	0.99-1.04	0.216			
TNFα	1.00	0.99-1.01	0.789			
IL-6	1.00	0.99-1.00	0.870			
NT-proBNP	1.00	1.00-1.00	0.970			
SF pain	0.95	0.92-0.98	**0.006**			
SF general health	0.96	0.93-0.99	**0.037**			
MCS	1.01	0.98-1.05	0.322			
PCS	0.98	0.96-1.01	0.240			
NYHA class	2.77	1.63-4.7	**<0.001**			
HAM-A	1.0	0.97-1.03	0.622			
HAM-D	1.00	0.97-1.03	0.819			

EF: Ejection fraction, GFR: Glomerular Filtration Rate, NLR: Neytrophile to Lymphocyte ratio, hs-CRP: High sensitive C-reactive protein, TNFα: Tumor necrosis factor alfa, IL-6: Interleukin-6, NT-proBNP: N-terminal pro-brain natriuretic peptide, SF: Short Form for quality of life, MCS: mental composite health score, PCS: Physical composite health score NYHA: New York Heart Association, HAM-D: Hamilton D rating scale, HAM-A: Hamilton A rating scale.

Table 5 Cox regression analysis for hospitalization

	Univariate			Multivariate		
Variable	**HR**	**CI 95%**	**p**	**HR**	**CI 95%**	**p**
Age (years)	1.04	1-1.07	**0.02**			
EF	0.95	0.91-0.99	**0.034**			
GFR	0.99	0.97-1	0.231			
Sodium	0.97	0.96-0.99	**0.006**	0.97	0.95-0.99	**0.006**
NLR	1.25	1-1.05	**0.011**	1.32	1.06-1.65	**0.012**
hsCRP	1.01	0.99-1.03	0.157			
TNFalfa	1.00	0.99-1.01	0.166			
IL-6	1.00	0.99-1.01	0.866			
NT-proBNP	1.00	1.00-1.00	0.885			
SF pain	0.96	0.93-0.99	**0.03**			
SF general healh	0.97	0.94-1.00	0.131			
MCS	0.95	0.91-0.99	**0.035**			
PCS	1.01	0.98-1.05	0.322			
NYHA class	2.47	1.47-4.16	**0.001**	2.48	1.37-4.48	**0.003**
HAM-A	1.02	1.00-1.05	**0.036**	1.04	1.01-1.07	**0.010**
HAM-D	1.02	1.00-1.05	**0.049**			

EF: Ejection fraction, GFR: Glomerular Filtration Rate, NLR: Neytrophile to Lymphocyte ratio, hs-CRP: High sensitive C-reactive protein, TNFα: Tumor necrosis factor alfa, IL-6: Interleukin-6, NT-proBNP: N-terminal pro-brain natriuretic peptide, SF: Short Form for quality of life, MCS: mental composite health score, PCS: Physical composite health score NYHA: New York Heart Association, HAM-D: Hamilton D rating scale, HAM-A: Hamilton A rating scale.

Table 6 Correlation analysis between some parameters with EF and BNP

EF			BNP		
Variable	r	p	Variable	r	p
GFR	0.164	0.077	GFR	-0.233	0.021
BNP	-0.006	0.530	Hs-CRP	0.368	<0.001
Hs-CRP	-0.178	0.072	TNF-α	0.009	0.929
TNF-α	-0.050	0.605	IL-6	0.650	<0.001
IL-6	0.035	0.723	NLR	0.561	0.06
NLR	-0.218	0.002	MCS	0.094	0.436
MCS	-0.086	0.349	PCS	0.078	0.436
PCS	0.048	0.603	SF physiological function	0.235	0.017
HAM-D	-0.039	0.671	SF physiological role	0.187	0.059
HAM-A	0.007	0.942	SF pain	0.185	0.061

EF: Ejection fraction, GFR: Glomerular Filtration Rate, NT-proBNP: N-terminal pro-brain natriuretic peptide, hs-CRP: High sensitive C-reactive protein, TNFα: Tumor necrosis factor alfa, IL-6: Interleukin-6, NLR: Neytrophile to Lymphocyte ratio, MCS: mental composite health score, PCS: Physical composite health score HAM-D: Hamilton D rating scale, HAM-A: Hamilton A rating scale.

depression are related to increased mortality, the combination of systolic HF and depression has become a more important issue nowadays. In the HF population, some investigations have showed that patients with depression and anxiety have higher rates of mortality and morbidity [18]. Moomersteeg et al. [19] reported that depression, CRP, and TNF-α receptors are associated with higher mortality rates in a study including 104 patients with HFrEF. However, in that study, diabetes mellitus was more common in the cardiovascular death group. By contrast, some authors have reported that depression is not an independent predictor of cardiovascular mortality in patients with HF [20,21]. Pelle et al. [22] showed that anxiety and depression symptoms were not related to mortality and was an independent risk factor for hospitalization in a study including 662 patients with HFrHF aged 40 years. In that study, patients were already hospitalized for HF at beginning of the study, were younger, and had follow-up for 1 year. Recently, metaanalysis investigating the relation between anxiety, depression and all-cause mortality in HF patients showed that depression is an independent predictor. However, these meta-analyses including a mixed HF population for reduced, mildly-reduced and preserved EF. Last European Heart Failure Guideline emphasized the depression was related to poor outcomes and worse clinical status in HF patients [23]. Depression and anxiety worsen the symptoms of heart failure and diminish the quality of life. Controversial findings about depression and anxiety's influence on mortality in HF patients and ineffectiveness of antidepressant treatment on clinical outcome may related to HF types, comorbidities, drug-drug interactions, follow-up time and used different depression scales. In our study, we included patients with compensated HFrEF-HFmrEF and the follow-up period was longer than other studies. We found that the depression and anxiety scores were related to hospitalization (HR 1.025 and 1.029, respectively) in the univariate analysis. Anxiety was an independent predictor of repeated hospitalization in our study population.

In most of the studies on depression, inflammatory markers, and HF, investigators used self-questioning scales such as the BDI scale, Patient Health Questionnaire depression module, and Center for Epidemiological Studies Depression-Scale for detecting depression or anxiety. Patients with both HF and depression suffer from reduced exertion tolerance, worsening quality of life, and poor NYHA functional capacity, which are symptoms present in both diseases. Some studies have suggested that depression is minimally related to an objective assessment of HF severity such as peak oxygen consumption, LVEF, and BNP levels; however, it significantly affected symptoms of HF such as NYHA capacity or results of the 6-minute walk test [24,25]. Therefore, we preferred HAM-D and HAM-A scales because they are applied through face-to-face interviews by a specialist and provide an objective assessment of symptoms. Different from previous studies, we used HAM-D and HAM-A to evaluate the presence of depression and anxiety scale by an interview with a physiatrist.

The relationship between the inflammation system and cardiovascular disease is widely known. Neutrophils play a role in the HF process because it is reflected in the pro-inflammatory status. NLR is a worse outcome biomarker for patients with high-risk status. Studies suggest that both HF is characterized by low-grade chronic inflammation [26,27]. In our study, NLR was significantly increased in non-survivors. It was related to a 1.3-fold risk increase for mortality in the univariate regression analysis and a 1.21-fold independent risk increase for hospitalization in the multivariate regression analysis. In this study, NLR of ≥2.68 is related to decreasing survival rates in the Kaplan–Meier analysis. In addition, we found a significant correlation between LVEF and NLR. These results emphasized that NLR reflects a low-grade inflammatory status in patients with HFrEF and HFmrEF.

Although increased CRP relates to new, recurring, or long-term depression, the relationship between inflammation and depression is unclear. While some studies suggested that depression and associated autonomic dysfunction might prolong immune activation and resulted in an inflammatory state in patients with HF, others have suggested that increased inflammation might worsen depressive symptoms [28,29].

TNF is a cytokine that promotes inflammation that activates immune cells. Studies have reported that serum IL-6 and TNF-α levels correlated with HF symptoms and poor prognosis [30,31]. Some authors have found that TNF-α receptor but not TNF-α level was related to cardiovascular mortality in their study [32]. Parissis et al. [33] found no relationship between serum IL-6 and TNF-α levels and cardiovascular outcomes; only IL-10 and BNP levels were independent predictors of cardiovascular mortality at 1-year follow-up in patients with HF and hospitalized. In our study serum BNP, TNF-α, hs-CRP, and IL-6 levels are not associated with cardiovascular mortality and hospitalization. Different results of previous studies may be related to the patient's LVEF because of the inflammation appears more prominent in HFpEF patients, functional capacity, compensated or non-compensated status, and immune-compromised status because of aging.

NT-proBNP is an indicator of volume overload as well as a diagnostic biomarker of HF. BNP level is related to the severity of HF and cardiovascular outcomes [34]. In our study, serum BNP levels were not related to cardiovascular mortality and hospitalization. It significantly correlated with IL-6 and hs-CRP levels like in previous studies [35].

This study has limitations. First, limited number of patients and the follow-up period were relatively short. Second, serum inflammatory levels and psychological assessments were evaluated only at baseline. Third, we did not re-evaluate serum biomarkers and LVEF during the study period. Finally, we evaluated functional capacity with an interview and not with the 6-minute walk test.

Conclusion

This study revealed that depression and anxiety are not related to cardiovascular mortality in HFrEF and HFmrEF patients. However, anxiety is an independent predictor for hospitalization. The levels of serum BNP, IL-6, TNF-, and hs-CRP are not associated to cardiovascular outcomes. NLR is related to repeated hospitalization.

Declaration of congress abstract: This study was presented as an 'poster presentation' at Heart Failure 2019 - 6th World Congress on Acute Heart Failure.

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: The study was supported by the Research Fund of the Çanakkale Onsekiz Mart University (project No TSA-2014-342).

Funding: The study was supported by the Research Fund of the Çanakkale Onsekiz Mart University (project No TSA-2014-342).The research sponsors did not participate in the study design, data collection, analysis, and interpretation, not involved in the writing of the manuscript, and the decision to submit the manuscript for publication

References

1. Haworth JE, Moniz-Cook E, Clark AL, Wang M, Waddington R, Cleland JG. Prevalence and predictors of anxiety and depression in a sample of chronic heart failure patients with left ventricular systolic dysfunction. *Eur J Heart Fail.* 2005;7(5):803-8. https://doi.org/10.1016/j.ejheart.2005.03.001
2. Griez EJ, Mammar N, Loirat JC, Djega N, Trochut JN, Bouhour JB. Panic disorder and idiopathic cardiomyopathy. *J Psychosom Res.* 2000;48(6):585-7. https://doi.org/10.1016/s0022-3999(00)00140-9
3. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. *J Am Coll Cardiol.* 2006;48(8):1527-37. https://doi.org/10.1016/j.jacc.2006.06.055
4. Rector TS. A conceptual model of quality of life in relation to heart failure. *J Card Fail.* 2005;11(3):173-6. https://doi.org/10.1016/j.cardfail.2004.09.002
5. Reynolds SL, Haley WE, Kozlenko N. The impact of depressive symptoms and chronic diseases on active life expectancy in older Americans. *Am J Geriatr Psychiatry*. 2008;16(5):425-32. https://doi.org/10.1097/JGP.0b013e31816ff32e
6. Sherwood A, Blumenthal JA, Trivedi R, Johnson KS, O'Connor CM, Adams KF Jr, et al. Relationship of depression to death or hospitalization in patients with heart failure. *Arch Intern Med.* 2007;167(4):367-73. https://doi.org/10.1001/archinte.167.4.367
7. Jiang W, Kuchibhatla M, Clary GL, Cuffe MS, Christopher EJ, Alexander JD, et al. Relationship between depressive symptoms and long-term mortality in patients with heart failure. Am Heart J. 2007;154(1):102-8. https://doi.org/10.1016/j.ahj.2007.03.043
8. Pelle AJ, Pedersen SS, Schiffer AA, Szabó B, Widdershoven JW, Denollet J. Psychological distress and mortality in systolic heart failure. *Circ Heart Fail.* 2010;3(2):261-7. https://doi.org/10.1161/CIRCHEARTFAILURE.109.871483
9. Torre-Amione G. Immune activation in chronic heart failure. *Am J Cardiol*. 2005;95(11A):3C-8C; discussion 38C-40C. https://doi.org/10.1016/j.amjcard.2005.03.006
10. Sun M, Chen M, Dawood F, Zurawska U, Li JY, Parker T, et al. Tumor necrosis factor-alpha mediates cardiac remodeling and ventricular dysfunction after pressure overload state. *Circulation*. 2007;115(11):1398-407. https://doi.org/10.1161/CIRCULATIONAHA.106.643585
11. Penninx BW, Kritchevsky SB, Yaffe K, Newman AB, Simonsick EM, Rubin S, et al. Inflammatory markers and depressed mood in older persons: results from the Health, Aging and Body Composition study. *Biol Psychiatry*. 2003;54(5):566-72. https://doi.org/10.1016/s0006-3223(02)01811-5
12. Bremmer MA, Beekman AT, Deeg DJ, Penninx BW, Dik MG, Hack CE, et al. Inflammatory markers in late-life depression: results from a population-based study. *J Affect Disord*. 2008;106(3):249-55. https://doi.org/10.1016/j.jad.2007.07.002
13. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* 1960;23(1):56-62. https://doi.org/10.1136/jnnp.23.1.56
14. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol.* 1959;32(1):50-5. https://doi.org/10.1111/j.2044-8341.1959.tb00467.x
15. Ware J E, Kosinski M. SF-36 Physical & Mental Health Summary Scales: A Manual for Users of Version 1. Second ed. Lincoln, Rohode Island: QualityMetric; 2001.
16. Ghosh RK, Ball S, Prasad V, Gupta A. Depression in heart failure: Intricate relationship, pathophysiology and most updated evidence of interventions from recent clinical studies. *Int J Cardiol*. 2016;224:170-77. https://doi.org/10.1016/j.ijcard.2016.09.063
17. Williams SA, Kasl SV, Heiat A, Abramson JL, Krumholz HM, Vaccarino V. Depression and risk of heart failure among the elderly: a prospective community-based study. *Psychosom Med*. 2002;64(1):6-12. https://doi.org/10.1097/00006842-200201000-00002
18. Jünger J, Schellberg D, Müller-Tasch T, Raupp G, Zugck C, Haunstetter A, et al. Depression increasingly predicts mortality in the course of congestive heart failure. *Eur J Heart Fail.* 2005;7(2):261-7. https://doi.org/10.1016/j.ejheart.2004.05.011
19. Mommersteeg PMC, Schoemaker RG, Naudé PJW, Eisel ULM, Garrelds IM, Schalkwijk CG, et al. Depression and markers of inflammation as predictors of all-cause mortality in heart failure. *Brain Behav Immun.* 2016;57:144-50. https://doi.org/10.1016/j.bbi.2016.03.012
20. Shen BJ, Xu Y, Eisenberg S. Psychosocial and Physiological Predictors of Mortality in Patients of Heart Failure: Independent Effects of Marital Status and C-Reactive Protein. Int J Behav Med. 2017;24(1):83-91. https://doi.org/10.1007/s12529-016-9579-2
21. Pelle AJ, Pedersen SS, Schiffer AA, Szabó B, Widdershoven JW, Denollet J. Psychological distress and mortality in systolic heart failure. *Circ Heart Fail.* 2010;3(2):261-7. https://doi.org/10.1161/CIRCHEARTFAILURE.109.871483
22. Freedland KE, Carney RM, Rich MW, Steinmeyer BC, Skala JA, Dávila-Román VG. Depression and Multiple Rehospitalizations in Patients With Heart Failure. *Clin Cardiol.* 2016;39(5):257-62. https://doi.org/10.1002/clc.22520
23. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, et al. ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599-3726. https://doi.org/10.1093/eurheartj/ehab368
24. Gottlieb SS, Kop WJ, Ellis SJ, Binkley P, Howlett J, O'Connor C et al. HF-ACTION Investigators. Relation of depression to severity of illness in heart failure (from Heart Failure And a Controlled Trial Investigating Outcomes of Exercise Training [HF-ACTION]). *Am J Cardiol*. 2009;103(9):1285-9. https://doi.org/10.1016/j.amjcard.2009.01.025
25. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2011 update: a report from the American Heart Association. *Circulation*. 2011;123(4):e18-e209. https://doi.org/10.1161/CIR.0b013e3182009701
26. Mann DL. Innate immunity and the failing heart: the cytokine hypothesis revisited. *Circ Res*. 2015;116(7):1254-68. https://doi.org/10.1161/CIRCRESAHA.116.302317

27. Horckmans M, Ring L, Duchene J, Santovito D, Schloss MJ, Drechsler M, et al. Neutrophils orchestrate post-myocardial infarction healing by polarizing macrophages towards a reparative phenotype. *Eur Heart J*. 2017;38(3):187-197. https://doi.org/10.1093/eurheartj/ehw002
28. Kop WJ, Synowski SJ, Gottlieb SS. Depression in heart failure: biobehavioral mechanisms. *Heart Fail Clin*. 2011;7(1):23-38. https://doi.org/10.1016/j.hfc.2010.08.011
29. Valkanova V, Ebmeier KP, Allan CL. CRP, IL-6 and depression: a systematic review and meta-analysis of longitudinal studies. *J Affect Disord*. 2013;150(3):736-44. https://doi.org/10.1016/j.jad.2013.06.004
30. Högye M, Mándi Y, Csanády M, Sepp R, Buzás K. Comparison of circulating levels of interleukin-6 and tumor necrosis factor-alpha in hypertrophic cardiomyopathy and in idiopathic dilated cardiomyopathy. *Am J Cardiol*. 2004;94(2):249-51. https://doi.org/10.1016/j.amjcard.2004.03.078
31. Deswal A, Petersen NJ, Feldman AM, Young JB, White BG, Mann DL. Cytokines and cytokine receptors in advanced heart failure: an analysis of the cytokine database from the Vesnarinone trial (VEST). *Circulation.* 2001;103(16):2055-9. https://doi.org/10.1161/01.cir.103.16.2055
32. Moorman AJ, Mozaffarian D, Wilkinson CW, Lawler RL, McDonald GB, Crane BA, et al. In patients with heart failure elevated soluble TNF-receptor 1 is associated with higher risk of depression. *J Card Fail*. 2007;13(9):738-43. https://doi.org/10.1016/j.cardfail.2007.06.301
33. Parissis JT, Farmakis D, Nikolaou M, Birmpa D, Bistola V, Paraskevaidis I, et al. Plasma B-type natriuretic peptide and anti-inflammatory cytokine interleukin-10 levels predict adverse clinical outcome in chronic heart failure patients with depressive symptoms: a 1-year follow-up study. *Eur J Heart Fail*. 2009;11(10):967-72. https://doi.org/10.1093/eurjhf/hfp125
34. Redwine LS, Mills PJ, Hong S, Rutledge T, Reis V, Maisel A, et al. Cardiac-related hospitalization and/or death associated with immune dysregulation and symptoms of depression in heart failure patients. *Psychosom Med.* 2007;69(1):23-9. https://doi.org/10.1097/PSY.0b013e31802e2f35
35. Johansson P, Lesman-Leegte I, Svensson E, Voors A, van Veldhuisen DJ, Jaarsma T. Depressive symptoms and inflammation in patients hospitalized for heart failure. *Am Heart J*. 2011;161(6):1053-9. https://doi.org/10.1016/j.ahj.2011.03.011