Türk Kardiyol Dern Arş - Arch Turk Soc Cardiol 2012;40(8):699-705 doi: 10.5543/tkda.2012.22058

Serum homosistein düzeyinin ileri sistolik kalp yetersizliği olan hastalarda bir yıllık sağkalımı öngörmedeki değeri

The value of serum homocysteine level in predicting one-year survival in patients with severe systolic heart failure

Dr. Ahmet Selami Tekin, Dr. Cihan Şengül,# Dr. Barış Kılıçaslan, Dr. Olcay Özveren,* Dr. Güliz Kozdağ†

Medeniyet University, Clinics of Cardiology, Göztepe Training and Research Hospital, İstanbul;
#Private Gaziosmanpaşa Hospital, Clinics od Cardiology, İstanbul;
*Yeditepe University, Faculty of Medicine, Clinics of Cardiology, Istanbul
†Kocaeli University, Faculty of Medicine, Clinics of Cardiology, Kocaeli

ÖZET

Amaç: Kalp yetersizliği (KY) temel bir halk sağlığı problemi olup önemli derecede mortalite ve morbiditeye neden olmaktadır. Bu nedenle sağkalım belirteçlerinin KY tedavisini yönlendirmedeki önemleri giderek artmaktadır. Son zamanlarda yayımlanan bazı çalışmalarda, kan homosistein düzeyleri KY gelişimi için yeni bir risk faktörü olarak bildirilmektedir. Çalışmamızda serum homosistein düzeyinin KY'li hastaların sağkalımını öngörmedeki değerini araştırdık.

Çalışma planı: Çalışmaya, sol ventrikül ejeksiyon fraksiyonu <%35 olan KY'li 70 hasta (44 erkek, 26 kadın; ort. yaş 60±12; dağılım 28-83 yıl) alındı. Klinik, ekokardiyografik ve biyokimyasal parametreler çalışma başlangıcında ölçüldü ve tüm hastalar izlemeye alındı. Kardiyak nedenli ölüm çalışmanın sonlanım noktası olarak kabul edildi.

Bulgular: On iki aylık izlem süresi sonunda hastaların 14'ü (%20) öldü. Ölen hastaların serum homosistein düzeyi sağ kalan hastalara kıyasla anlamlı düzeyde yüksekti (20.8±5.8 ve 16.9±5.1 µmol/l, p=0.029). Serum homosistein düzeyinin >17.45 µmol/l olması %71.4 özgüllük ve %67.9 duyarlılık oranları ile 1 yıl sonunda

ABSTRACT

Objectives: Heart failure (HF) is a major public health problem responsible for high morbidity and mortality rates. Thus, the importance of survival predictors in directing the treatment of HF is gradually increasing. In some recently published studies, plasma homocysteine has been reported as a newly recognized risk factor for the development of HF. In the present study, we investigated the value of serum homocysteine levels in predicting the survival of patients with HF.

Study design: Seventy HF patients (44 males, 26 females; mean age 60±12; range 28 to 83 years) with left ventricle ejection fractions of <35% were included in our study. Clinical, echocardiographic, and biochemical parameters were measured at baseline, and all patients were followed. Cardiac death was established as the end point of the study.

Results: At the end of the 12 month follow-up period, 14 patients (20%) had died. Serum homocysteine levels were significantly higher in the deceased patients compared to the patients who survived (20.8±5.8 vs. 16.9±5.1 µmol/l, p=0.029). A serum homocysteine level of >17.45 µmol/l predicted death at the end of the first year with 71.4% specificity and

gelişen ölümleri uygun kestirim değeri ile saptadı (ROC eğrisi altındaki alan: 0.855, %95 GA 0.792-0.965, p<0.001). Çok değişkenli Cox regresyon analizinde serum homosistein düzeyi sağkalımın tek belirteci olarak saptandı.
Sonuç: Serum homosistein düzeyi KY bulunan hastalarda orta dönemde mortalitenin önemli bir belirteci olabilir.

67.9% sensitivity (ROC area under curve: 0.855, CI 95% 0.792-0.965, p<0.001). Multivariate Cox regression analysis showed that the serum homocysteine level was the only parameter predicting survival.
Conclusion: Serum homocysteine level may be an important predictor of mid-term mortality in patients with HF.

Abbreviations:

BNP *Brain natriuretic peptide*
EF *Ejection fraction*
hs-CRP *high-sensitivity C-reactive protein*
CAD *coronary artery disease*
HF *heart failure*
NYHA *New York Heart Association*

Despite increased treatment options, heart failure (HF) results in high rates of mortality, and morbidity.[1]

Many clinical researches have found a correlation between higher plasma homocysteine levels, and thrombotic, and vascular atherosclerotic diseases.[2,3] However, recent studies have revealed hyperhomocysteinemia as a new risk factor for the development of HF.[4] It has been suggested that higher homocysteine levels impair endothelium-mediated vasodilation, and exert negative inotropic effects on myocardium resulting in the development, and progression of HF.[5,6] Herman et al. [7] reported increases in serum homocysteine levels in parallel with the severity of HF. In an analysis performed on participants enrolled in the Framingham Heart Study, increased homocysteine levels was found to be related to higher risks of HF even in patients without any current, and past evidence of heart attack.[8] However, scarce number of studies have reported that homocysteinemia predicts mortality in patients with HF.[9,10]

In the present study, the effects of plasma homocysteine levels on cardiac mortality in patients with HF have been evaluated at the end of the first year of the follow-up period.

Geliş tarihi: 21.02.2012 Kabul tarihi: 22.08.2012
Yazışma adresi: Dr. Cihan Şengül. Özel Gaziosmanpaşa Hastanesi, Kardiyoloji Kliniği, 34245 Gaziosmanpaşa, İstanbul.
Tel: +90 212 - 615 38 38 e-mail: drcsengul@yahoo.com

Submitted on: 02.21. 2012 Accepted for publication on: 08.22. 2012
Address of correspondence: Dr. Cihan Şengül. Özel Gaziosmanpaşa Hospital, Clinics of Cardiology, 34245 Gaziosmanpaşa, İstanbul.
Phone: +90 212 - 615 38 38 e-mail: drcsengul@yahoo.com

PATIENTS AND METHOD

This study was performed on 70 patients with HF (44 males, 26 females, mean age, 60 ± 12 yrs; range, 28-83 years) who were hospitalized in the cardiology service or consulted to our out-patient clinics with ejection fractions (EF) of < 35 % who had undergone coronary angiographic examinations. The study was approved by the Ethics Committee of our hospital, and informed undersigned consent forms were obtained from all patients.

Patients receiving Vitamin B derivatives, and fibrates which are known to effect plasma homocysteine levels, and cases with serum creatinine levels above 2 mg/dL were excluded from the study.

Detailed medical history of all patients was obtained, and physical examinations were performed. The drugs they had been using, their daily dosages, blood pressure measurements, and demographic data of all patients were recorded. After a 12-hour fasting period venous blood samples were drawn into blank or citrated tubes. Blood samples were analyzed as for glucose, total cholesterol, triglyceride, HDL-, and LDL-cholesterol, calcium, uric acid, high-sensitivity C-reactive protein (hs-CRP), urea, creatinine, brain natriuretic peptide (BNP), hematological parametres, and sedimentation rates. Besides, thyroid function tests were performed. Creatinine clearance was calculated using Cockcroft-Gault formula. Serum samples were frozen, and stored at -80^{o}C for further measurement of homocysteine levels Homocysteine was measured in IMMUNILITE 2000 device (DPC Diagnostic, LA, USA) using a chemiluminescence method.

All patients underwent standard 2-D echocardiographic examinations using Vivid 7 echocardiography device with 2.5 MHz transducer. Left atrial diameter, dimensions of the left ventricle (LV), interventricular septum, and posterior wall thickness were measured. LVEFs were calculated with modified Simpson's method using measurements obtained from 4-chamber views. All measurements were based on the standards proposed by by American Association of Echocardiography.[11]

Clinical class of the heart failure was determined according to NYHA (New York Heart Association) criteria. The patients were monitored from the first day of their enrollment in the study. Clinical follow-up was achieved by phone calls, and periodic examinations performed in our clinics. All the patients were monitored for a mean follow-up period of 12.6±1.8 months (range 7-15 mos). The endpoint of our study was determined as cardiac mortality.

Table 1. Demographic data, clinical characteristics, and laboratory test results of the patients

	n	%	Mean ± SD
Mean age (yrs)			60±12
Male / Female	44 / 26		
BMI kg/m^2.			26±4
NYHA clinical class			
I	14		
II	35		
III	21		
SBP (mmHg)			115±15
DBP (mmHg)			74±8
ECG: sinus rhythm/AF	60 / 10		
Jugular venous distension	16		
Edema	7		
Echocardiographic findings			
Ejection fraction (%)			26±8
LVEDD (mm)			66±8
LVESD (mm)			53±9
Left atrium (mm)			46±7
Laboratory values			
Homocysteine (µmol/l)			17.7±5.4
BNP (pg/ml) [median (range)]			588 (2770-
hs-CRP (mg/dl) [median (range)]			38) 0.9 (10.4-
Hemoglobin (g/l)			12.5±1.6
Creatinine clearance (ml/min)			70±20
Potassium (mEq/l)			4.3±0.5
Cardiac risk factors			
Smokers		14	
Hypertension		39	
Coronary artery disease		66	
Diabetes mellitus		37	
Medications			
Beta-blockers		61	
Diuretics		53	
ACE-inhibitors		84	
ARB s		14	
Digoxin		34	
Aspirin		83	
Nitrates		19	
Statins		51	

SD: standard deviation; BMI: Body mass index; SBP: Systolic blood pressure; DBP: diastolic blood pressure; NYHA: New York Heart Association; ECG: Electrocardiogram AF: Atrial fibrillation EF: Ejection fraction; LVEDD: Left ventricular end-diastolic diameter; LVESD: Left ventricular end-systolic diameter; BNP: Brain natriuretic peptidet; hs-CRP: High sensitivity C-reactive protein; CAD Coronary artery disease; ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker.

Table 2. Mean values of the deceased, and survived patients

	Survived patients (n=56)		Deceased patients (n=14)		*p*
	%	Mean ± SD	%	Mean ± SD	
Gender (male)	66		50		0.266
Age (yrs)		59±12		66±13	0.045
Follow-up period (mos)		12.8±1.6		11.9±2.3	0.247
Body mass index		26±4		27±5	0.747
kg/m^2	63		79		0.352
Hypertension	38		43		0.713
Diabetes mellitus	36		43		0.621
SBP (mmHg)		115±15		117±14	0.622
DBP (mmHg)		73±8		74±9	0.963
Medications					
ACE-inhibitor	82		93		0.442
Beta-blocker	64		50		0.326
LVEF		26±8 66±9		24±9	0.412
LVEDD				63±5	0.239
LVESD (mm)		53±10		49±4	0.130
Hemoglobin (g/l)		12.6±1.6		12.3±1.3	0.445
hs-CRP (mg/dl) [median (range)]		1.8 (10.4-0.8)		1.9 (6.4-0.1)	0.464
Creatinine clearance (ml/min)		76±18		60±14	0.207
Sodium (mEq/l)		139±3.8		138±5.6	0.883
Potassium (mEq/l)		4.35±0.51		4.28±0.41	0.508
Homocysteine (µmol/l)		16.9±5.1		20.8±5.8	0.029
BNP (pg/ml) [median (range)]		395 (680-38)		576 (2770-240)	0.079

SD: Standard deviation; SBP: Systolic blood pressure; DBP: diastolic blood pressure; LV EF: Left ventricular ejection fraction; LVEDD: Left ventricular end-diastolic diameter; LVESD: Left ventricular end-systolic diameter; BNP: Brain natriuretic peptide; hs-CRP: High sensitivity C-reactive protein; CAD Coronary artery disease; ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker.

Statistical Analysis

SPSS (Statistical Package for Social Sciences) package program v. 11.0 was used for the evaluation of the study data. Descriptive statistical data were expressed as standard deviation, median (max., and min.) for continuous, and percentages for categoric variables. For categoric variables *chi*-square test, and Fisher's exact test, and for continuous variables Mann-Whitney U-test were used. Cut-off value was determined using ROC (receiver operating characteristic) curve analysis. Risk factors that might be related to mortality, and uneventful survival (age, hypertension, hemoglobin, creatinine, BNP, homocysteine levels, EF, current, and past history of diabetes) were investigated using univariate Cox

regression analysis. Parametres with p values below 0.05 were included in the multivariate Cox regression analysis. The results were evaluated within 95 % confidence interval (CI). P <0.05 was considered as statistically significant.

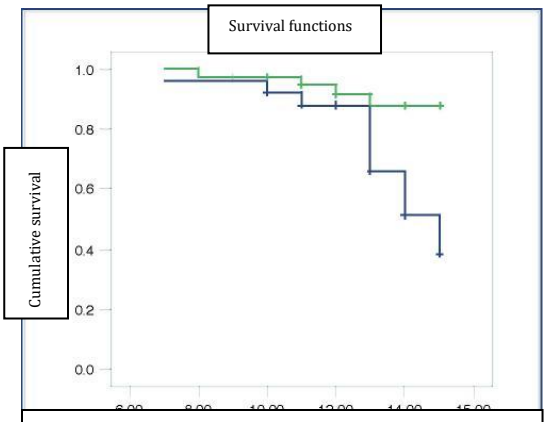

Figure 1. Kaplan-Meier curve adjusted for age, cardiac death, and sudden death based on cut-off value of homocysteine level

RESULTS

The patients had either ischemic (n=24) or nonischemic (n=24) dilated cardiomyopathy, coronary artery disease (CAD: n= 46; 66 %), hypertension (HT: n=27; 39 %), and diabetes mellitus (DM: n=10; 14 %), while 10 (14 %) participants were smokers.

Table 3. Comparative analysis of the patients based on serum homocysteine threshold value

	Increased serum homocysteine level		Decreased serum homocysteine level		*p*
	%	Mean ± SD	%	Mean ± SD	
Gender (male)	73		55		0.139
Age (yrs)		66±9		55±12	**<0.001**
Follow-up period (mos)		12±1.8		11.9±2.5	0.447
Coronary artery disease	76		57		0.09
Hypertension	36		40		5
Diabetes	33	118±13	40	112±15	0.56
SBP(mmHg)					8
DBP (mmHg)		74±7		72±9	0.472
Medications					
ACE-inhibitor	90		80		0.255
Beta-blocker	63	24±8	60	27±7	0.77
LVEF (%)					7
LVEDD (mm)		65±6		65±8	0.80
LVESD (mm)		51±7		53±10	3
Hemoglobin (g/l)		12.3±1.8		12.6±1.4	0.428
hs-CRP (mg/dl) [median (range)]		0.93 (5.7-0.1)		0.9 (10.4-0.1)	0.603
Sodium (mEq/l)		139±4		138±4	0.678
Potassium (mEq/l)		4.34±0.44		4.33±0.52	0.906
BNP (pg/ml) [median (range)]		610 (2770-74)		566 (2010-38)	0.731
Cardiac death	41		8		**<0.001**
Sudden death	20		10		**<0.001**

SD: Standard deviation; SBP: Systolic blood pressure; DBP: diastolic blood pressure; LV EF: Left ventricular ejection fraction; LVEDD: Left ventricular end-diastolic diameter; LVESD: Left ventricular end-systolic diameter; BNP: Brain natriuretic peptidet; hs-CRP: High sensitivity C-reactive protein; CAD Coronary artery disease; ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker.

According to NYHA criteria, the patients were classsified as class I (n=14; 20 %), II (n=35; 50 %) III (n=21; 30%). Since the patients were included in the study after stabilization of their clinical status, none of them were in the NHYA class IV.

Table 4. Univariate analysis of mortality

	HR	95 % CI	*p*
Age	1	0.99-1.11	0.05
Hypertension	1.2	0.38-4.104	0.713
Diabetes	1.3	0.41-4.44	0.621
Hemoglobin	0.8	0.82-1.2	0.550
Creatinine	5.8	0.77-44.6	0.086
BNP	1	0.99-1.0	0.460
LVEF	0.9	0.89-1.03	0.311
Homocysteine	1.1	1.0-1.2	0.02

HR: Hazard ratio; CI: Confidence interval; LVEF: Left ventricular ejection fraction; BNP: Brain natriuretic peptide

Table 5. Multivariate analysis of homocysteine level, and age

	OR	95 %CI	*p*
Homocysteine	1.1	1.02-1.27	0.021
Age	1.1	0.9-1.2	0.091

OR: Odds ratio; CI: Confidence interval

ECGs of the patients revealed sinus rhythm in 60 (84 %), and atrial fibrillation in 10 patients. Twenty four (34 %) patients had left bundle branch block. A total of 7 (10%) patients carried an implantable cardiac defibrillator (ICD), while cardiac resynchronization therapy (CRT) was not applied in any patient.

The patients were receiving aspirin (n=58; 83%), angiotensin converting enzyme (ACE) inhibitor (n=59; 84 %), angiotensin receptor blocker (ARB) (n=43; 61 %), beta-blocker (n=43; 61 %), furosemide (n=49; 70 %), spironolactone (n=49; 57 %), digoxin (n=24; 34 %), a thiazide diuretic (n=39; 43 %), nitrate (n=13; 19 %), and a statin (n=36; 51%). Other demographic, clinical characteristics, and laboratory test results are shown in Table 1.

During the the follow-up period 14 (20%) patients were lost because of cardiac mortality. Four patients were lost because of deterioration of their HF, and inadequate cardiac pumping function, and also sudden death (n=10; 14 %) during their monitorization in the intensive care unit. . Any significant difference was not found between deceased, and survived patients as for the presence of CAD, HT, DM, smoking status, NYHA categories of HF, and clinical parametres as anemia, jugular vein distension, edema, ECG rhythm, LVEF, hypopotassemia, and hypercreatininemia. Homocysteine levels, and ages detected in deceased patients were higher than those survived. Mean age of the deceased was 66±13 years, while of the survived patients it was 59±12 years (p=0.045). Mean serum homocysteine value in patients who died of cardiac death was 20.8±5.8 μmol/l, while it was 16.9±5.1 μmol/l in those survived. (Table 2). Mean serum homocysteine value in patients suffered from sudden death was significantly higher than that of those survived (19.8±4.8 μmol/l *vs* 16.9±5.1 μmol/l, respectively; p=0.035).

Correlation analyses demonstrated a moderately positive correlation between serum homocysteine level, and age of the

patients (p=0.001, r=0.397) but a weakly positive correlation was detected between these levels, and creatinine clearance values (p=0.015, r=0.298). However, any correlation did not exist between homocysteine levels, and EF (p=0.087, r=-0.211) or BNP (p=0.975, r=0.004)

When cut-off value for serum homocysteine level was accepted as 17.45 μmol/l, number of deaths that might happen within 1 year could be predicted with 71.4 % specificity, and 67.9 % sensitivity. (area under ROC: 0.855, 95% CI 0.792-0.965, p<0.001). Based on this cut-off value, the patients were divided into two comparative groups (Table 3). Patients with serum homocysteine levels above this cut-off value, were older with significantly higher rates of cardiac or sudden death. Kaplan-Meier survival curve constructed based on this cut-off value is seen in Figure 1. In univariate Cox regression analysis, serum homocysteine level was found to be significantly influential on mortality (p=0.02) (Table 4). The impact of age on mortality had a borderline significance (p=0.053). In multivariate regression analysis, when serum homocysteine levels, and age were evaluated in combination, only homocysteine levels had a significant effect on mortality (Table 5).

DISCUSSION

The results of our study reinforce the importance of increased serum homocysteine levels as a predictive factor of mid-term mortality in patients with HF secondary to ischemic, and nonischemic dilated cardiomyopathy.

Homocysteine is a sulphur containing amino acid produced by demethylation of methionine.[12] Both clinical, and epidemiological studies have demonstrated that increased homocysteine levels is an independent risk factor for cardiovascular diseases.[2,3,13,14] Thus, in order to decrease the incidence of cardiovascular diseases, homocysteine-lowering treatment modalities were proposed, however relevant investigations had yielded controversial outcomes.[15,16]

Many publications have asserted that higher homocysteine levels might be an important risk factor also in our community. Two studies have demonstrated hyperhomocysteinemia as a potentially critical cardiovascular risk factor for our community.[17,18] An investigation aimed to determine homocysteine levels in the Turkish population detected median homocysteine level as 11.1 μmol/L in healthy individuals without any cardiovascular disease.[19] In our study, detection of median homocysteine level as 17.7 μmol/l both in ischemic, and non-ischemic HF patients, supports the results of the investigations suggesting homocysteine as a risk factor in cardiac dysfunction apart from atherothrombosis.

Limited number of studies have suggested that higher homocysteine levels lead to perivascular, and interstitial fibrosis resulting in loss of myocardial elasticity, and also contribute to the cardiac remodelling.[5,20] Besides, based on many case reports, homocysteine decreases effectiveness of myocardial pump function.[6] With these effects, homocysteine appears to have an impact on the progression of chronic HF.

Increases in serum homocysteine levels with the severity of HF have been demonstrated.[7] Gibelin et al.[9] reported correlations between higher serum homocysteine levels, and severity of the disease independent of the etiology of HF, and determined its predictive value as for mortality. Indeed, our study has arrived at similar conclusions comparable with these studies. Homocysteine levels of the patients deceased at the end of the first year of the follow-up period were significantly higher.

It has been reported that homocysteine widens QRS interval, and leads to interstitial fibrosis in cardiac tissues.[21] Besides, increased homocysteine levels also demonstratedly cause conduction disorders.[22] By means of these mechanisms homocysteine conceivably might lead to deaths caused by cardiac arrhytmias.[23] Some studies have also demonstrated correlations between homocysteine levels, and sudden cardiac death secondary to coronary plaque rupture.[24] Outcomes of our study tend to support the potential role of higher homocysteine levels in sudden death. Results of our study revealed significantly higher mean serum homocysteine levels in patients lost because of sudden death when compared with those survived. Similarly, comparisons based on homocysteine cut-off values demonstrated higher rates of sudden death in patients with increased homocysteine levels

Previously, many studies have reported that a correlation existed between BNP levels, and prognosis of HF patients.[25] Even though BNP levels in deceased patients were higher relative to survived patients in our study, difference between groups did not reach statistical significance. In our study, very wide spectrum of BNP levels, small number of patients, and relatively shorter follow-up period (median 12.6 months) might prevent emergence of a significant difference between the groups.

Even though patients with clinical conditions which are known to effect serum homocysteine levels were not included in our study, inability to measure vitamin B12, and folic acid levels of all patients is an important limitation of our study. Shorter follow-up period of the patients (median 12.6 months), and relatively scarce number of our patients when compared with other studies investigating the mid-term prognosis of HF patients is another limitation of our study.

In conclusion, higher serum homocysteine levels are detected to be a predictor of mid-term mortality in patients with advanced HF. As an outcome of larger scale randomized studies with a treatment arm conducted in the future, the relationship between homocysteine, and chronic HF should be more clearly revealed, and the issue of whether or not homocysteine-lowering treatments alter mortality, and morbidity rates of HF should be resolved.

Conflict of interest: None declared

REFERENCES

1. Van Jaarsveld CH, Ranchor AV, Kempen GI, Coyne JC, van Veldhuisen DJ, Sanderman R. Epidemiology of heart failure in a community-based study of subjects aged > or = 57 years: incidence and long-term survival. Eur J Heart Fail 2006;8:23-30.
2. Van Guelpen B, Hultdin J, Johansson I, Witthöft C, Weinehall L, Eliasson M, et al. Plasma folate and total homocysteine levels are associated with the risk of myocardial infarction, independently of each other and of renal function. J Intern Med 2009;266:182-95.
3. Nygård O, Nordrehaug JE, Refsum H, Ueland PM, Farstad M, Vollset SE. Plasma homocysteine levels and mortality in patients with coronary artery disease. N Engl J Med 1997;337:230-6.
4. Sundström J, Vasan RS. Homocysteine and heart failure: a review of investigations from the Framingham Heart Study. Clin Chem Lab Med 2005;43:987-92.
5. Vizzardi E, Bonadei I, Zanini G, Fiorina C, Raddino R, Dei Cas L. Homocysteine: a casual link with heart failure?. [Article in Italian] Minerva Med 2009;100:421-7. [Abstract]
6. Kennedy RH, Owings R, Shekhawat N, Joseph J. Acute negative inotropic effects of homocysteine are mediated via the endothelium. Am J Physiol Heart Circ Physiol 2004;287:H812-7.
7. Herrmann M, Kindermann I, Müller S, Georg T, Kindermann M, Böhm M, et al. Relationship of plasma homocysteine with the severity of chronic heart failure. Clin Chem 2005;51:1512-5.
8. Vasan RS, Beiser A, D'Agostino RB, Levy D, Selhub J, Jacques PF, et al. Plasma homocysteine and risk for congestive heart failure in adults without prior myocardial infarction. JAMA 2003;289:1251-7.
9. Gibelin P, Serre S, Candito M, Houcher B, Berthier F, Baudouy M. Prognostic value of homocysteinemia in patients with congestive heart failure. Clin Chem Lab Med 2006;44:813-6.
10. Naruszewicz M, Jankowska EA, Zymlinski R, Bukowska H, Millo B, Banasiak W, et al. Hyperhomocysteinemia in patients with symptomatic chronic heart failure: prevalence and prognostic importance-pilot study. Atherosclerosis 2007;194:408-14.
11. Henry WL, DeMaria A, Gramiak R, King DL, Kisslo JA, Popp RL, et al. Report of the American Society of Echocardiography Committee on Nomenclature and Standards in Two-dimensional Echocardiography. Circulation 1980;62:212-7.
12. Malinow MR. Homocyst(e)ine and arterial occlusive diseases. J Intern Med 1994;236:603-17.
13. Bostom AG, Selhub J. Homocysteine and arteriosclerosis: subclinical and clinical

disease associations. Circulation 1999;99:2361-3.

14. Eikelboom JW, Lonn E, Genest J Jr, Hankey G, Yusuf S. Homocyst(e)ine and cardiovascular disease: a critical review of the epidemiologic evidence. Ann Intern Med 1999;131:363-75.

15. Zhou YH, Tang JY, Wu MJ, Lu J, Wei X, Qin YY, et al. Effect of folic acid supplementation on cardiovascular outcomes: a systematic review and meta-analysis. PLoS One 2011;6:e25142.

16. Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group, Armitage JM, Bowman L, Clarke RJ, Wallendszus K, Bulbulia R, et al. Effects of homocysteine-lowering with folic acid plus vitamin B12 vs placebo on mortality and major morbidity in myocardial infarction survivors: a randomized trial. JAMA 2010;303:2486-94.

17. Tokgözoğlu SL, Alikaşifoğlu M, Atalar E, Aytemir K, Özer N, Ünsal İ ve ark. Homosistein ve MTHFR genotipinin koroner arter hastalığı risk ve yaygınlığının belirlenmesindeki önemi. Türk Kardiyol Dern Arş 1999;27:598-603.

18. Aksoy M, Öç M, Aksoy ŞN, Koldaş M, Mihmanlı MB, Yazıcıoğlu MV ve ark. Bir Türk kohortunda plazma homosistein, folat ve B12 vitamini düzeyinin koroner arter hastalığı risk faktörü olarak önemi. Türk Kardiyol Dern Arş 2000;28:481-8.

19. Aksoy ŞN, Geyikli İ, Saygılı Eİ. Sağlıklı kişilerde plazma homosistein düzeyinin belirleyicileri. Türk Biyokimya Dergisi 2006;31;175-81.

20. Mendes RH, Sirvente RA, Candido GO, Mostarda C, Salemi VM, D'Almeida V, et al. Homocysteine thiolactone induces cardiac dysfunction: role of oxidative stress. J Cardiovasc Pharmacol 2010;55:198-202.

21. Miller A, Mujumdar V, Palmer L, Bower JD, Tyagi SC. Reversal of endocardial endothelial dysfunction by folic acid in homocysteinemic hypertensive rats. Am J Hypertens 2002;15:157-63.

22. Podrid PJ, Myerburg RJ. Epidemiology and stratification of risk for sudden cardiac death. Clin Cardiol 2005;28:I3-11.

23. Givvimani S, Qipshidze N, Tyagi N, Mishra PK, Sen U, Tyagi SC. Synergism between arrhythmia and hyperhomo-cysteinemia in structural heart disease. Int J Physiol Pathophysiol Pharmacol 2011;3:107-19.

24. Burke AP, Fonseca V, Kolodgie F, Zieske A, Fink L, Virmani R. Increased serum homocysteine and sudden death resulting from coronary atherosclerosis with fibrous plaques. Arterioscler Thromb Vasc Biol 2002;22:1936-41.

25. Berger R, Huelsman M, Strecker K, Bojic A, Moser P, Stanek B, et al. B-type natriuretic peptide predicts sudden death in patients with chronic heart failure. Circulation 2002;105:2392-7.

Anahtar sözcükler: Homosistein/kan; kalp yetersizliği/kan; natriüretik peptit, beyin; sağkalım oranı; Türkiye.

Key words: Homocysteine/blood; heart failure/blood; natriuretic peptide, brain; survival rate; Turkey.