Ischemic stroke history predicts increased cardiovascular mortality in chronic heart failure

İskemik inme öyküsü, kronik kalp yetersizliğinde artmış kardiyovasküler mortaliteyi öngördürür

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ABSTRACT

Objective: To investigate comorbidities that predict cardiac mortality and re-hospitalization in chronic heart failure (CHF) patients.

Methods: Five hundred eighty patients (mean age 63±13 years, 373 male, 207 female, mean ejection fraction (EF) 26±9%) with mild, moderate or severe CHF [NYHA class II-IV] were included in this prospective observational study. We evaluated all comorbidities such as history of ischemic stroke, coronary artery disease, peripheral arterial disease, chronic obstructive lung disease, hypertension, diabetes mellitus and chronic kidney disease in CHF patients who were hospitalized due to decompensated heart failure in Kocaeli University, Faculty of Medicine's Hospital between January 2003 and July 2009. Cox regression and Kaplan-Meier survival analyses were used to establish predictors of unfavorable outcomes.

Results: Of 580 patients 207 (36%) patients died due to cardiovascular reasons. In multivariable Cox regression analysis age (HR-1.06, 95% CI 1.04-1.08, p<0.001), NYHA functional class (HR-3.20 95% CI, 1.90-5.41, p<0.001), history of ischemic stroke (HR-2.48, 95% CI 1.14-5.37, p=0.022), high-sensitive C-reactive protein (HR-1.09, 95% CI, 1.04-1.15, p=0.001), brain natriuretic peptide (HR-1.00, 95% CI 1.00-1.00, p=0.01) and hemoglobin (HR-0.90, 95% CI 0.81-0.99, p=0.038) were independent predictors of cardiac death in the present study. History of ischemic stroke was demonstrated as an important comorbidity that predicts cardiovascular mortality beyond other co-morbidities in CHF patients. NYHA functional class (HR-2.85, 95% CI 1.80-4.65, p<0.001), left ventricular EF [(HR-0.98, 95% CI 0.95-0.99, p=0.039) and ischemic stroke history (HR-2.41, 95% CI 1.15-5.05, p=0.019) were independent predictors for recurrence hospitalization. The stroke history was only predictor showing recurrent hospitalization at least in one year among the other comorbid conditions, which were evaluated during study.

Conclusion: History of ischemic stroke may be an important risk factor for increased cardiac mortality and recurrence hospitalization in CHF patients. *(Anadolu Kardiyol Derg 2011; 11: 421-7)*

Key words: Chronic heart failure, ischemic stroke, mortality, survival, regression analysis

ÖZET

Amaç: Kronik kalp yetersizliği (KKY) hastalarında kardiyak mortalite ve tekrarlayan hastaneye yatışları öngören komorbidite durumları araştırmak.

Yöntemler: Hafif, orta ve ciddi (NYHA sınıfı II-IV) KKY'li 580 hasta (ortalama yaş 63±13 yıl, 373 erkek, 207 kadın, ortalama ejeksiyon fraksiyon (EF) %26±9) bu prospektif gözlemsel çalışmaya dahil edildi. Çalışmamızda dekompanse kalp yetersizliği nedeniyle Ocak 2003 ve Temmuz 2009 tarihleri arasında Kocaeli Üniversitesi, Tıp Fakültesi hastanesine yatırılan KKY'li hastalarda mevcut olan tüm komorbidite durumları; iskemik inme, koroner arter hastalığı, periferik arter hastalığı, kronik obstrüktif akciğer hastalığı, hipertansiyon, diyabetes mellitus ve kronik böbrek yetersizliği öyküsünü değerlendirdik. İstenmeyen sonlanım olayların öngödürücüleri Cox regresyon ve Kaplan-Meier sağkalım analizleri ile belirlendi.

Bulgular: Toplam 580 hastadan 207 (%36) hasta kardiyovasküler nedenlerden dolayı öldü. Çoklu Cox regresyon analizinde yaş (HR-1.06, %95 GA %95 GA 1.04-1.08, p<0.001), NYHA fonksiyonel kapasite, (HR-3.20, %95 GA 1.90-5.41, p<0.001), iskemik inme öyküsü (HR-2.48,%95 GA 1.14-5.37, p=0.022), hs-CRP (HR-1.09, %95 GA 1.04-1.15, p=0.001), BNP (HR-1.00, %95 GA 1.00-1.00, p=0.01) ve hemoglobin (HR-0.90, %95 GA 0.81-0.99, p=0.038) kardiyak ölüm için bağımsız öngördürücü olarak saptandı. KKY'li hastalarda iskemik inme öyküsü diğer komorbidite durumlara göre

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kardiyovasküler mortaliteyi daha iyi öngördürdü. NYHA fonksiyonel kapasite (HR-2.85, %95 GA 1.80-4.65, p<0.001), sol ventrikül ejeksiyon fraksiyonu (HR-0.98,%95 GA 0.95-0.99, p=0.039) ve iskemik inme öyküsü (HR-2.41, %95 GA 1.15-5.05, p=0.019) tekrarlayan hastaneye yatışlar için bağımsız öngördürücü olarak saptandı. İskemik inme öyküsü çalışmada değerlendirilen diğer komorbidite durumlara nazaran en az bir yıl içerisinde tekrarlayan hastaneye yatışları öngördüren tek komorbidite durumdu.

Sonuç: İskemik inme öyküsü KKY'li hastalarda artmış kardiyovasküler mortalite ve tekrarlayan hastaneye yatışlar için önemli bir risk faktörü olabilir. *(Anadolu Kardiyol Derg 2011; 11: 421-7)*

Anahtar kelimeler: Kronik kalp yetersizliği, iskemik inme, mortalite, sağkalım, regresyon analiz

Introduction

Chronic heart failure (CHF) is a major and growing public health problem resulting from the cardiac damage caused a variety of disease processes (1, 2). These processes are dominated by coronary artery disease (CAD) in Western countries (1). Heart failure is a leading and expanding cause of morbidity and mortality in the world today (3). CHF, which is characterized by decreased left ventricular ejection fraction (LVEF) has higher annual mortality rate than 40%, particularly among those with severe left ventricular dysfunction (4). Many patients sustain sudden death, thought to be secondary to occlusive coronary thrombosis (5-8). CHF has many comorbid conditions such as hypertension (HT), CAD, peripheral artery disease, chronic renal disease. Comorbidity is defined as a chronic condition that coexists in an individual with another condition (9). Those conditions are well known worldwide chronic diseases. Some comorbid conditions contribute to its etiology such as CAD, HT and diabetes mellitus (DM). Moreover, 40% of the patients had more than 5 non-cardiac comorbidities. The five most common non-cardiac comorbidities are HT (55%), DM (31%), chronic obstructive pulmonary disease (26%), ocular disorders (24%) and hypercholesterolemia (21%) (10).

Our purpose was to understand, which comorbidity of CHF is the most important predictor for cardiac death and recurrent hospitalization in patients with CHF. What were the characteristics of patients who have the strongest comorbid predictor on mortality of CHF?

Methods

Study population

Five hundred eighty patients with dilated cardiomyopathy have been evaluated between January 2003 and July 2009. All study population was admitted in Cardiology Clinic of Kocaeli University, Faculty of Medicine's Hospital during their worsening heart failure period. A total of 580 patients (373 male, 207 female, mean age 63±13 years, New York Heart Association (NYHA) functional class II-IV) with the diagnosis of ischemic and non-ischemic dilated cardiomyopathy were included in the study. In this prospective observational study we evaluated all comorbidities such as history of ischemic stroke, CAD, peripheral arterial disease, chronic obstructive lung disease, HT, DM and chronic kidney disease in CHF patients. Diagnosis of dilated cardiomyopathy was based on the transthoracic echocardiographic findings of left ventricular end-diastolic diameter >56

mm and dysfunctional left ventricle (LV) with ejection fraction (EF) <45%. All patients were evaluated with diagnostic coronary angiography for determining the etiology of the heart failure if they have had no previous coronary angiography (Table 1). Exclusion criteria were as follows: severe aortic stenosis and mitral stenosis with patients who had symptoms of decompensated heart failure.

The study was conducted in accordance with the Declaration of Helsinki and approved by local institutional Ethics Committee. All patients gave informed consent prior to study entry.

Table 1. Basal characteristics of chronic heart failure patients

Gender, male, n (%)	373 (64)
Age, years	63±13
NYHA functional class, n (%)	
II	137 (24)
III	412 (71)
IV	31 (5)
Blood pressure, mmHg	125/81
Ischemic stroke, n (%)	33 (6)
Peripheral arterial disease, n (%)	87 (15)
Chronic obstructive lung disease, n (%)	81 (14)
Hypertension, n (%)	429 (74)
Diabetes mellitus, n (%)	197 (34)
Chronic kidney disease, n (%)	151 (26)
Coronary artery disease, n (%)	365 (63)
Medication, n (%)	
Aspirin	516 (89)
Clopidogrel	99 (17)
Warfarin	122 (21)
Beta blocker	412 (71)
ACE-I/ARB	481 (83)
Statin	360 (62)
Ejection fraction, %	26±9
BNP, pg/mL	1166±1007
hs-CRP, mg/mL	2.5±3.8
Creatinine, mg/mL	1.5±3.8

Data are presented as mean±standard deviation and number (percentage)
ACE-I/ARB - angiotensin-converting enzyme inhibitors/angiotensin-II receptor blockers, BNP - brain natriuretic peptide, hs - CRP-high sensitive-C reactive protein, NYHA - New York Heart Association

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Echocardiographic assessment

All participants underwent transthoracic echocardiography using an echocardiograph equipped with a broadband transducer (Vivid 7, GE Vingmed, and Horten, Norway). Measurements of the left atrium, left ventricle and right ventricle were obtained from parasternal long axis and apical four chamber view according to standard criteria. LVEF was calculated using the modified Simpson's rule in the apical 2- and 4-chamber views. Mitral flow was measured from the apical 4-chamber view with pulsed wave (PW) Doppler by placing the sample volume at the tips of mitral leaflets.

Blood samples

Fasting blood samples were drawn from a large antecubital vein in each patient for determination of biochemical and hemostatic parameters during the first 1-3 days of hospitalization. Brain natriuretic peptide (BNP) levels were measured with by the commercially available Triage® BNP test (Biosite Incorporated, San Diego, California, USA) which is a fluorescence immunoassay for the quantification of BNP in 24 hours. Serum high-sensitive C-reactive protein (hs-CRP), was measured by a sensitive nephelometric assay (Image 800 Immunochemistry System, Beckman Coulter, LA, USA). Sedimentation, albumin, creatinine, hemoglobin and lipid levels were measured by standard methods.

Patient follow-up

Follow-up was started on the first day of hospitalization. Clinical follow-up was done by phone contact and periodical examination of patients in the outpatient clinic. All patients were followed for a mean duration of 39±14 months (12-78 months). Primary endpoint of the study was cardiac death including sudden death and death attributable to advanced heart failure. Secondary endpoint was recurrence hospitalization due to worsening of heart failure.

Statistical analysis

All statistical analyses were performed with the SPSS 13.0 (SPSS Inc., Chicago, IL, USA) statistical software package program. Results are presented as mean±SD or as percentages and numbers for categorical data. In comparison of the patients with and without end points of the study, continuous variables that were normally distributed were analyzed with 2- tailed t test and unequally distributed variables were analyzed with Mann-Whitney U test. Categorical data and proportions were analyzed using Chi-square (χ^2).

Clinical and laboratory parameters were compared between the patients with and without end-points during the follow-up period. The resulting, parameters which had been evaluated in the model consisted of parameters which were significantly different between event positive and negative groups. Cox proportional hazard analysis was used to assess independent predictors of survival. A p value less than 0.05 was considered as statistically significant. Comorbid conditions were CAD, DM, HT, chronic obstructive lung disease, peripheral arterial disease and history of ischemic stroke in the study group. History of ischemic stroke, chronic kidney disease, HT, age, NYHA functional class, hemoglobin, BNP and CRP levels, patient's LVEF were included as independent predictors for cardiac death in Cox regression analysis. The Kaplan-Meier survival curve was used to analyze the timing of events during follow-up. NYHA functional class, BNP levels, patient's LVEF and history of ischemic stroke were included in the Cox regression analysis model to determine the independent predictors for recurrence hospitalization.

Results

Predictors of cardiac death in CHF patients

Two hundred seven (36%) patients died due to cardiovascular reasons. Non-survived patients were older than survived patients (<0.001). Non-survivors had higher NYHA functional class, increased hs-CRP levels and BNP levels, decreased hemoglobin levels, lower EF and higher rates of history of ischemic stroke, chronic kidney disease and HT compared to survivors (p<0.05 for all) (Table 2).

In multivariable Cox regression analysis, age (HR-1.06, 95% CI 1.04-1.08, p<0.001), NYHA functional class (HR-3.20, 95% CI 1.90-5.41, p<0.001), history of ischemic stroke (HR-2.48, 95% CI 1.14-5.37, p=0.022), hs-CRP (HR-1.09, 95% CI 1.04-1.15, p=0.001), BNP (HR-1.00, 95% CI 1.00-1.00, p=0.01) and hemoglobin (HR-0.90, 95% CI 0.81-0.99, p=0.038) were independent predictors for cardiac death in the present study.

Table 2. Clinical and laboratory characteristics of non-survivors and survivors

Variables	Non-survivors (n=207)	Survivors (n=373)	*p
NYHA functional class	3.1±0.4 3.0 (2.0-4.0)	2.7±0.5 3.0 (2.0-4.0)	<0.001
Age, years	69±11 71 (22-94)	60±13 62 (18-86)	<0.001
Brain natriuretic peptide, pg/mL	1385±1124 963 (109-5000)	1044±915 741 (114-5000)	<0.001
hs-CRP, mg/dL	3.3±4.6 1.4 (0.03-27.5)	2.1±3.2 0.8 (0.01-19.7)	<0.001
Hemoglobin, g/dL	12.3±1.9	12.9±1.9	<0.001
Ejection fraction, %	24.6±9.8	26.4±9.0	0.026
Left atrial dimension, mm	47±7	46±7	NS
History of stroke, n (%)	20 (1)	13 (0.3)	0.002
Chronic kidney disease, n (%)	68 (33)	81 (22)	0.003
History of hypertension, n (%)	164 (79)	265 (71)	0.031

Data are presented as mean ±standard deviation or number (percentage), median (min-max) values
*unpaired Student's t, Chi-square and Mann-Whitney U tests
hs-CRP - high sensitive C reactive protein, NS - non-significant, NYHA - New York Heart Association

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Among all comorbidities, only history of ischemic stroke was demonstrated as an independent predictor of cardiovascular mortality and worse survival in CHF patients (Table 3).

Characteristics of patients with history of ischemic stroke

Overall, 33 patients had ischemic stroke history, including 20 (61%) patients with stroke history of the study group who died due to cardiac reason, while 187 (34%) patients died follow up period had no history of stroke (p=0.002) (Fig. 1). Patients with ischemic stroke history were older as compared to patients without ischemic stroke history in the study (p=0.031) (Table 4). Although diastolic blood pressure was higher in patients with stroke history than those without stroke history it could not reach statistical significance (p=0.067). History of HT and

Table 3. Multivariate Cox proportional regression analysis of predictors for cardiac death

Variables	HR	95%CI	p
Age	1.06	1.04-1.08	<0.001
NYHA class	3.20	1.90-5.41	<0.001
Ischemic stroke history	2.48	1.14-5.37	0.022
hs-CRP	1.09	1.04-1.15	0.001
Hemoglobin	0.90	0.81-0.99	0.038
BNP	1.00	1.00-1.00	0.010

BNP - brain natriuretic peptide, hs-CRP-high sensitive C - reactive protein, NYHA - New York Heart Association

Table 4. Clinical characteristics of patients with and without ischemic stroke history

Variables	Patients with ischemic stroke history (n=33)	Patients without ischemic stroke history (n=547)	*p
NYHA functional class	3.0±0.3 3 (2-4)	2.8±0.5 3 (2-4)	<0.001
Age, years	67±10	63±13	0.031
Systolic blood pressure, mmHg	128±18	125±19	NS
Diastolic blood pressure, mmHg	80±12	76±12	0.067
Brain natriuretic peptide, pg/mL	1146±866	1167±1015	NS
hs-CRP, mg/dL	2.5±3.4	2.5±3.8	NS
Ejection fraction, %	25.6±8.9	26.0±9.4	NS
Left atrial dimension, mm	47.7±9.4	46.4±6.8	NS
History of hypertension, n (%)	33/429 (8)	0/151 (0)	<0.001
History of peripheral artery disease, n (%)	13/85 (15)	20/195 (4)	<0.001
Jugular venous distention, n (%)	27/329 (8)	6/251 (2)	0.003

Data are presented as mean±standard deviation or number (percentage), median (min-max) values
*unpaired Student's t, Chi-square and Mann-Whitney U tests
hs - CRP - high sensitive-C reactive protein, NS - non-significant, NYHA - New York Heart Association

peripheral artery disease were significantly higher in patients with ischemic stroke history compared to in patients without ischemic stroke history (p<0.001 for both) (Table 4).

Patients who were NYHA functional class III had higher stroke history according to those who were NYHA II (8% vs. 3%, p=0.003). It seems that patients with ischemic stroke history had prevalent CAD. Patients who had three coronary vessels disease have had higher stroke history than patients who had no CAD (8% vs. 3%, p=0.034).

LVEF, left ventricular dimensions, left atrial dimension, presence of chronic kidney disease, presence of atrial fibrillation, hemoglobin levels, creatinine levels, BNP and hs-CRP levels did not show any differences between patients with stroke and patients without stroke in CHF patients (Data not shown).

Predictors of re-hospitalization in patients with CHF

One hundred-forty seven (25%) patients were hospitalized because of decompensated heart failure at least in one year. Patients who had recurrence hospitalizations were older than patients without recurrence hospitalizations. Patients with recurrence hospitalization had higher NYHA functional class, higher levels of BNP, lower LVEF and history of ischemic stroke compared to without recurrence hospitalization due to decompensated heart failure in univariate analysis (p<0.05) (Table 5).

NYHA functional class (HR-2.85, 95% CI 1.80-4.65, p<0.001), LVEF (HR-0.98, 95% CI 0.95-0.99, p=0.039) and ischemic stroke history (HR-2.41, 95% CI 1.15-5.05, p=0.019) were independent predictors for recurrence hospitalization at least during one year. The stroke history was only statistically significant predictor for recurrent hospitalization among comorbid conditions (Table 6).

In long-term period comorbid conditions did not predict recurrent hospitalization.

Discussion

In our study classic markers of poor prognosis in CHF such as increased age, NYHA functional class, hemoglobin level, hs-CRP levels found as predictors of poor prognosis in study group. Although CHF has many comorbid conditions presence of ischemic stroke predicted the worst outcome beside HT, chronic kidney disease, in multivariate Cox regression analysis. Presence of ischemic stroke also predicted recurrent hospitalization according to other comorbid conditions. Patients with history of ischemic stroke had increased age, worse functional status and worse signs of heart failure, prevalent CAD, history of HT and history of peripheral artery disease in the study.

Prevalence of HT was 55-76% of heart failure population in previous studies (10-12). Our population had similar prevalence rate of HT with above mentioned studies. HT was the most prevalent comorbidity in our study as Episerve study. HT was one of the reasons of cardiac mortality in CHF patients. Many of the reports accomplished that the most important etiology of
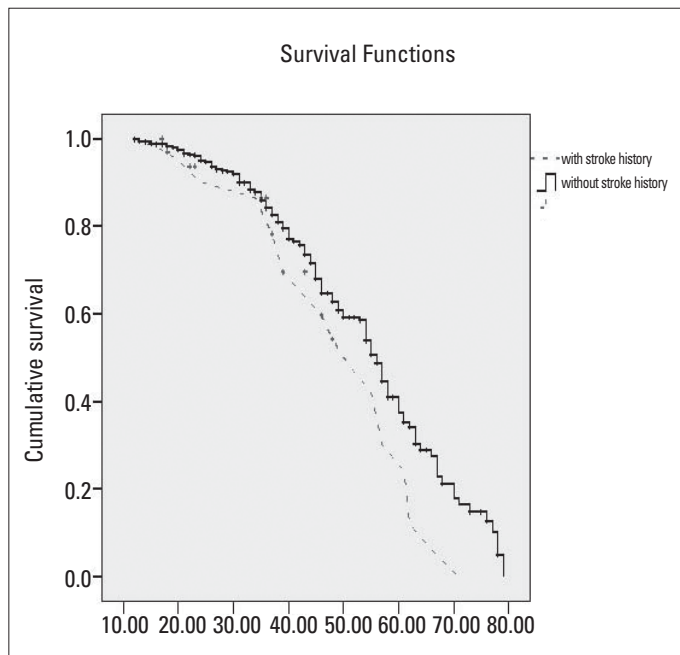
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Figure 1. Kaplan-Meier survival analysis of chronic heart failure patients according to presence of ischemic stroke history (p=0.022)

Table 5. Clinical characteristics of patients with and without re-hospitalization

Variables	Hospitalized patients (n=147)	Non-hospitalized patients (n=433)	*p
NYHA functional class	3.03±0.50	2.74±0.50	<0.001
Age, years	65±11	63±13	0.047
Brain natriuretic peptide, pg/mL	1518±1116	1046±939	<0.001
hs-CRP, mg/dL	2.5±3.7	2.5±3.8	NS
Ejection fraction,%	23.2±9.4	26.6±9.2	<0.001
History of ischemic stroke, n (%)	15 (1)	18 (0.4)	0.006
History of chronic lung disease, n (%)	28 (19)	55 (12)	0.058

Data are presented as mean±standard deviation or number (percentage)
*unpaired Student's t and Chi-square tests
hs-CRP - high-sensitive C-reactive protein, NS - non-significant, NYHA - New York Heart Association

Table 6. Multivariate Cox proportional regression analysis of predictors for recurrent hospitalization

Variables	HR	95% CI	p
NYHA Class	2.85	1.80-4.65	<0.001
Ischemic stroke history	2.41	1.15-5.05	0.019
Ejection fraction	0.98	0.95-0.99	0.039

NYHA - New York Heart Association

heart failure is coronary heart disease. However, many of the patients who have coronary heart disease have had HT in their history (13). Although HT is one of the most important risk factor for the development of heart failure it was found that higher blood pressure was associated lower mortality rate than isch-

emic heart disease (14). However systolic and diastolic blood pressure was not different between patients who died due to cardiac reasons or those patients who were survival, presence of HT history was one of the reasons which showed cardiac mortality in our study group.

Approximately 40% of CHF patients have chronic renal disease (15). Many primary CHF patients have evidence of renal dysfunction in the absence of intrinsic renal disease. The low glomerular filtration rate in CHF is an effect of decreased cardiac output, with low renal perfusion and intrarenal vasoconstriction which is accompanied by sodium and water retention (9). It was reported that renal dysfunction was an adverse prognostic marker in patients with CHF as in our study (15).

Although CHF has have an annual incidence of 2-4% thromboembolic stroke (16) it was reported that stroke is the third most common cause of death in European countries, accounting for high mortality in both the short and long term. Presence of previous cardiac disease and cardioembolic stroke was determined as predictors of long term mortality in survival after first ever stroke event (17-19). Recently heart failure has attracted considerable interest as potential risk factor for increased morbidity and mortality after stroke. Left ventricular dysfunction, even mild, was shown to be independently associated with an increased risk of ischemic stroke (20). Presence of heart failure anticipated poor outcome for mortality and cardiovascular morbidity after acute stroke (21, 22). Koton et al. (23) have shown that CHF was one of the predictors of long term mortality for patients surviving the first month after stroke. In our study group the existence of ischemic stroke history was the independent predictor for the cardiac mortality. Patients with ischemic stroke also have had more recurrent hospitalization than without stroke history in the study group. Our findings have supported the result of previous studies which was mentioned above. The rising incidence of CHF has increased probability of stroke events. After stroke event heart failure patients have worse prognosis and lower life expectancy according to those without stroke event.

In present study, one of the mortality risks of severe CHF patients was the existence of ischemic stroke history. Patients with ischemic stroke also have had more recurrent hospitalization than without stroke history in the study group. To our knowledge patients with AF is associated with greater mortality and morbidity in patients with ischemic stroke than those without AF (16, 24-26). Unfortunately in our study AF was not found significantly a risk factor for ischemic stroke CHF patients. These findings could be explained by existence of severe CHF may hinder of AF to appear being as powerful predictor factor on ischemic stroke.

Increased age, existence of HT, presence of atherosclerotic disease such as CAD and peripheral artery disease has been well known risk factors for occurrence of ischemic stroke (27). Both systolic dysfunction and heart failure can be determined in patients with stroke after first index event or patients have been followed by diagnosis of CHF before occurrence of stroke (28).

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Age, presence of HT and prevalent atherosclerotic disease, symptoms and findings of advanced heart failure which were worse functional capacity and jugular vein distention were characteristics of patients with ischemic stroke in study group.

Study limitations

The occurrence of repeated stroke after index hospitalization in patients with CHF did not evaluate which was the limitation point of the study.

Conclusion

It is found that several comorbid conditions including history of ischemic stroke, chronic kidney disease and HT were important predictors for cardiovascular mortality beyond the worse functional status, older age, increased levels of BNP and hs-CRP and decreased level of hemoglobin. Presence of peripheral arterial disease in CHF patients may increase the occurrence of stroke or both may be manifestation of advanced atherosclerosis.

Clinical implications

It can be assumed that patients with CHF who have increased age, history of HT, prevalent atherosclerotic disease such as 3-vessel CAD and peripheral artery disease, advanced heart failure symptoms may have ischemic stroke as co-morbidity. It was reported that silent cerebral infarction which may be a pioneer for threatened stroke was common finding in MRI or CT in CHF patients (29). Usage of preventive strategies against ischemic stroke may have beneficial effect for CHF patients who have the above mentioned characteristics. It should be kept in mind by the physicians that CHF patients with a history of ischemic stroke had significantly more new hospitalizations than those without a history of stroke.

Conflict of interest: None declared.

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