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New-onset Atrial Fibrillation: An Independent Predictor of in-hospital Mortality in Reduced Ejection Fraction Heart Failure Patients

Düşük Ejeksiyon Fraksiyonlu Kalp Yetersizliği Hastalarında Hastane İçi Mortaliteyi Artıran Bağımsız Bir Belirteç Olarak Yeni Başlangıçlı Atriyal Fibrilasyon

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Abstract

Objectives: Heart failure (HF) is associated with high mortality and atrial fibrillation (AF) is the most common arrhythmia encountered in HF patients with reduced ejection fraction (EF). We aimed to assess whether new-onset AF is an independent poor prognostic factor in this group of patients. We also searched for parameters that might influence the in-hospital mortality in reduced EF heart failure (HFrEF) patients.

Materials and Methods: The study was a retrospective observational study investigating the admission characteristics and in-hospital events for 119 HFrEF patients at sinus rhytym, admitted for decompensated heart failure. We evaluated the in-hospital mortality and aimed to identify the predictive factors.

Results: Overall 12% of the heart failure patients died during hospitalization. The mean age of the study population was 71±9 years with 37% female. The mean EF was 27±7% and mean duration of hospitalization was 9±4 days. Patients with lower body mass index, lower glomerular filtration rate and patients with longer hospitalization had significantly higher in-hospital mortality rates (p=0.02, p=0.04 and p=0.001, respectively). New-onset AF, restrictive filling pattern and being angiotensin-converting enzyme inhibitors/angiotensin receptor blockers naive were factors significantly related to higher mortality (p=0.001, p=0.001 and p=0.02, respectively). Long hospitalization duration and new-onset AF at hospital were independent predictors of in-hospital mortality [p=0.006 Odds ratio (OR): 1.394 (1.098-1.771) and p=0.012 OR: 10.869 (2.677-71.428), respectively].

Conclusion: In hospital outcome of patients admitted with decompensated HFrEF is poor. In our trial, patients with new-onset AF and patients with longer hospitalization duration had higher mortality rates. An understanding of the risk factors for in-hospital deaths may help improving intensive care for this patient population.

Key Words: New Onset Atrial Fibrillation, Heart Failure Reduced Ejection Fraction, Mortality

Öz

Amaç: Kalp yetersizliği yüksek mortalite ile ilişkili olup, atriyal fibrilasyon (AF) düşük ejeksiyon fraksiyonlu kalp yetersizliği (HFrEF) hastalarında en sık görülen aritmidir. Çalışmamızda, bu hastalarda yeni başlangıçlı AF'nin bağımsız prognostik bir belirteç olup olmadığını araştırdık. Ayrıca, çalışmamızda HFrEF hastalarında hastane içi mortaliteyi etkileyen diğer parametreler de değerlendirildi.

Gereç ve Yöntem: Çalışmamız retrospektif, gözlemsel bir çalışmadır. Dekompanse kalp yetersizliği nedeniyle hastanemize kabul edilen sinüs ritmindeki 119 düşük ejeksiyon fraksiyonlu (EF) hasta yatış özellikleri, hastane içi olaylar ve mortalite açısından değerlendirilmiştir.

Bulgular: Hastaların %12'si hastane izlemi sırasında kaybedilmiştir. Hastaların ortalama yaşı 71±9 olup %37'si kadındır. Ortalama EF'si 27±7 olup ortalama hastanede yatış süresi 9±4 gündü. Düşük vücut kitle indeksi, düşük glomerüler filtrasyon hızı ve uzun hastane yatışı olan hastalar daha fazla hastane içi mortaliteye sahipti (sırasıyla; p=0,02, p=0,04 ve p= 0,001). Yeni başlangıçlı AF, restriktif doluş bozukluğu ve anjiyotensin enzim/reseptör inhibitörleri kullanmamak da yüksek hastane içi mortalite ile anlamlı olarak ilişkiliydi (sırasıyla; p=0,001, p=0,001 ve p=0,02). Uzun hastane yatışı ve yeni başlangıçlı AF hastane içi mortalite için bağımsız belirleyiciler olarak saptandı [sırasıyla p=0,006 Odds oranı (OR): 1,394 (1,0988-1,771] ve p=0,012 OR: 10,869 (2,677-71,428)].

Sonuç: Hastaneye dekompanse olarak kabul edilen HFrEF hastalarında prognoz kötüdür. Çalışmamızda yeni başlangıçlı AF ve uzamış hastane yatışının mortalite üzerine bağımsız olarak etki eden belirteçler olduğunu saptadık. Hastane içi ölümlere etki eden prognostik belirteçleri iyi saptayabilmek, bu hastalarda daha yoğun ve etkin hedefler için yardımcı olabilir.

Anahtar Kelimeler: Yeni Başlangıçlı Atriyal Fibrilasyon, Düşük Ejeksiyon Fraksiyonlu Kalp Yetersizliği, Mortalite

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Introduction

Heart failure (HF) is increasing in prevalence all over the world. Its most common form, reduced ejection fraction (EF) HF (HFrEF), is associated with significant mortality and morbidity due to pump dysfunction and arrhythmias. Atrial fibrillation (AF) is the most common associated arrhythmia, and it shows an increased incidence in HF compared with non-HF patients (1). AF has its mortality and morbidity burden, but it also accelerates the progression of HF and has an extra negative contribution to the ongoing disease state. New-onset AF was shown to double the annualized crude mortality rates in patients with advanced HF (2). However, there is no consistency in the literature about the unfavorable prognostic effect of AF in patients with HFrEF because of the need to adjust variables associated with worse outcomes. As a result, controversy remains about whether AF is an independent prognostic factor in this patient group (3,4).

Patients with HF experience nearly 1,100,000 hospitalizations yearly, and in-hospital mortality is still an understudied component of adverse HF outcomes (5). We aimed to investigate whether new-onset AF is a poor prognostic factor for in-hospital mortality. In addition, we evaluated the clinical and laboratory parameters for their potential effects on in-hospital mortality.

Material and Methods

Patients hospitalized for acute decompensated HF at Ankara University Shool of Medicine, Department of Cardiology from January 2017 to June 2018, were evaluated retrospectively. Patients both with dilated and ischemic cardiomyopathy were included in our study. Exclusion criteria were: 1) left ventricular EF >40%, 2) acute coronary syndrome, 3) hemodynamic instability like cardiogenic or septic shock and patients who needed cardiopulmonary resuscitation, 4) newly diagnosed HF (diagnosis <3 months), 5) patients with known AF or AF at admission, 6) end-stage renal failure [glomerular filtration rate (GFR)] <15 mL/min/1.73 m^2) or dialysis patients, and 7) patients with signs of active infection or sepsis.

The local ethics committee approved the study protocol (date: 10.10.2016, decision no: 15-756-16).

Patients' admission vital functions, laboratory data and echocardiographic parameters were noted to charts routinely, as well as their daily clinical progression and mortality reports if death occured. Admission laboratory values were used for statistical comparison. EF was measured by transthoracic echocardiography at admission and the modified Simpson method was used. Restrictive filling at echocardiography was determined according to the diastolic mitral inflow velocity patterns. The term, new-onset AF, included patients having AF during hospitalization and was diagnosed by 12 lead electrocardiography with at least 30 seconds of an AF rhythm trace. AF management and treatment were done according to the recent guidelines (6). The decompensated state was diagnosed according to the modified Framingham Criteria (7). Patients were managed according to the recent HF management guideline of the European Society of Cardiology (8). Patient characteristics and in-hospital data were compared between the two groups, patients with and without in-hospital mortality.

Statistical Analysis

Statistical analyses were performed using the SPSS software package (version 20 for Windows, SPSS Inc., Chicago, Illinois). Discrete variables were expressed as numbers and percentages, whereas continuous variables were expressed as means ± standard deviations. A chi-square analysis or Fisher's exact test was used for the categorical variables, and the Student's t-test or Mann-Whitney U test was performed for the continuous variables. A multivariable logistic regression analysis was performed to assess the independent predictors of in-hospital mortality. Gender, age, and variables with a $p<0.1$ in the univariate analysis were subjected to multivariate analysis. A probability value of $p<0.05$ was considered significant.

Results

One hundred and nineteen patients with normal sinus rhythm and HFrEF, hospitalized for decompensation were evaluated in our trial. The mean age of the study population was 71±9 years, with 37% of the female gender. The mean EF was 27±7% and the mean duration of hospitalisation was 9±4 days. Overall, 12% (n=14) of patients died during hospitalization. The main reasons for death were pulmonary edema (50%) and cardiogenic shock (29%). Other reasons were sepsis (14%) and lethal arrhythmic death (ventricular tachycardia/fibrillation) (7%). New-onset AF occured in 14 patients (11%) during the hospitalization. Electrical or medical cardioversion was performed in eight patients; two patients recovered to sinus rhythm medically by amiodarone, the others required electrical cardioversion (one was unsuccessful, and two relapsed during hospitalization). The remaining six patients were followed up with heart rate control. Drugs for rate control were mainly beta-blockers and digitalis if treatment with beta-blockers was not tolerated or not enough. The decision was made by the attending physician according to the clinical guidelines and patient status. A prophylactic low molecular weight heparin anticoagulant regimen was routinely applied in patients with decompensated HF, the dose was increased to therapeutic levels for patients with new onset-AF (7). During the hospitalization period, no patients had a stroke, hemorrhagic-complications, or digitalis toxicity as AF morbidity.

Baseline characteristics of patients according to in-hospital mortality, are given in Table 1. Patients with a ower body mass

index (BMI), lower GFR, and patients with longer hospitalization duration had significantly higher in-hospital mortality rates (p=0.02, p=0.04 and p=0.001, respectively). New-onset AF at hospital, restrictive filling pattern on echocardiography and being angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker (ACE-I/ARB) drugs naive were factors significantly related to higher in-hospital mortality (p=0.001, p=0.001 and p=0.02, respectively). In logistic regression analysis, long hospitalization duration and new-onset AF at hospital were independent predictors of in-hospital mortality [p=0.006 Odds ratio (OR): 1.394 (1.0988-1.771) and p=0.012 OR: 10.869 (2.677-71.428), respectively] (Table 2).

Table 1: Baseline clinical characteristics of study patients according to in-hospital mortality

	In hospital mortality (+) (n=14)	In hospital mortality (-) (n=105)	p value
Age, year mean ± SD	74±8	71±9	0.32
Women, n (%)	5 (36%)	39 (37%)	0.91
Body mass index (kg/m^2)	25±6	29±4	0.02
Hypertension, n (%)	7 (50%)	7 (50%)	0.52
Diabetes Mellitus, n (%)	8 (57%)	68 (65%)	0.57
Current smokers, n (%)	4 (29%)	19 (18%)	0.35
WBC at admission (10^9/L)	9.1±3.3	8.7±3.6	0.75
C-reactive protein, (mg/L)	30.5±37.4	22.9±24.6	0.31
Brain natriuretic peptide, (pg/mL)	1756±991	1429±890	0.22
GFR (mL/min/1.73 m^2)	40±18	51±19	0.04
Oxygen saturation (%) by probe	88±5	86±5	0.26
Systolic blood pressure on admission (mmHg)	96±28	110±26	0.10
New onset atrial fibrillation during hospitalization, n (%)	6 (43%)	8 (8%)	<0.001
NYHA class 4, n (%)	8 (%57)	49(%46)	0.69
Dilated cardiomyopathy, n (%)	2 (14%)	17 (16%)	0.85
Inotropic support during hospitalization, n (%)	4 (29%)	16 (15%)	0.21
Patients with ICD, n (%)	2 (27%)	14 (13%)	0.35
Hospitalization duration (day)	12±6	8±4	<0.001
Medications used on admission			
Statin, n (%)	7 (50%)	61(58%)	0.56
Angiotensin-converting enzyme inhibitors/ Angiotensin receptor blockers, n (%)	6 (43%)	77 (73%)	0.02
Beta blocker, n (%)	8 (57%)	79 (75%)	0.15
Ivabradine, n (%)	3 (21%)	19 (18%)	0.69
Echocardiographic parameters			
Restrictive pattern of filling, n (%)	9(64%)	24 (23%)	<0.001
Ejection fraction (%)	25±7	28±8	0.18
Pulmonary artery systolic pressure, mmHg	51±8	46±13	0.51

GFR: Glomerular filtration rate, ICD: Implantable cardioverter defibrillator, NYHA: New York Heart Association, WBC: White blood cells, SD: Standard deviation, n: Number

Table 2: Predictors of in hospital mortality by multivariate logistic regression analysis

	OR (95%, CI)	p value
Age	1.032 (0.951-1.121)	0.446
Male gender	1.335 (0.278-6.414)	0.718
BMI	0.924 (0.801-1.066)	0.279
Atrial fibrillation at hospital	10.869 (2.677-71.428)	0.012
Glomerular filtration rate	1.008 (0.968-1.050)	0.691
ACE/ARB use	0.361 (0.078-1.658)	0.191
Hospitalization duration	1.394 (1.098-1.771)	0.006
Restrictive filling pattern	2.941 (0.624-13.888)	0.172

ACE/ARB: Angiotensin-converting enzyme inhibitors/Angiotensin receptor blockers BMI: Body mass index, CI: Confidence interval, OR: Odds ratio

Discussion

In this cohort of 119 patients hospitalized for decompensation with HFrEF, the rate of in-hospital mortality was 12%. New-onset AF during hospitalization and longer hospitalization duration were the two independent factors negatively affecting the in-hospital mortality. To the best of our knowledge, this is the first study of an association between new-onset AF and in-hospital mortality of HFrEF patients.

AF is the most common arrhythmia in patients with HFrEF, and its presence increases the severity of HF. The prevalence of AF reaches up to 50% in patients with New York Heart Association functional class IV (9). In some studies, AF was shown to cause a poorer prognosis. However, results were not consistent after adjusting for other variables associated with worse outcomes. Mogensen et al. (10), analyzed 15,415 patients enrolled in two large trials (PARADIGM-HF and ATMOSPHERE) and evaluated the type of AF affecting the outcome of patients with HFrEF. New-onset AF was associated with the greatest risk of adverse events. In a trial that tested the hypothesis whether new-onset AF was related to HF progression, there was a 2-fold increase in mortality and a 4.5-fold increase in hospitalization burden in new-onset AF patients, at the 2-year follow up (2). This risk attributed to new-onset AF can be partially explained by established chronic AF in the setting of HF represents a selected survivor patient group. However, new-onset AF allows the detection of the adverse events prospectively (11). Multicenter Automatic Defibrillator Implantation Trial (MADIT-II), had also concluded the 2-fold

increase in mortality in HF patients with new-onset AF (12). The analysis of ACALM (Algorithm of Comorbidities, Associations, Length of stay and Mortality) registry, a comprehensive long-term registry of 1,000,000 patients, the coexistence of AF and HF was found to have the greatest all-cause mortality rate and longer hospital stay (13). In our trial, we searched for the effect of parameters and characteristics of HFrEF patients on the rate of in-hospital mortality, not long-term mortality. Our results, like the literature, showed the negative impact of new-onset AF on the in-hospital mortality. This negative impact was not attributed to side effects of drugs used for AF, because there were no hemorrhagic complications during anticoagulation or drug toxicity during rate and rhythm control. However, AF is known to reduce the cardiac output further because of the loss of atrial contribution (7). This may be the key contributing factor to increased events and eventually increased mortality rates. Besides the new-onset AF, longer hospitalization duration was also detected as an independent predictor. It could be predicted that patients with worse clinical progress and condition, would stay for longer times at the hospital, face to additional complications, and have higher mortality rates.

In a trial investigating the in-hospital mortality in acute decompensated HF patients, blood urea nitrogen level on admission, serum creatinine level, and low admission systolic blood pressure were found to be the best mortality predictors. A risk tree made according to parameters of 65,275 patients revealed in-hospital mortality ranging from 2.1% to 21.9% (14). This trial included HF patients with both reduced and preserved EF. It is known that important differences exist between these two groups of patients regarding clinical characteristics and in-hospital mortality (5). In our trial of patients with HFrEF and sinus rhythm on admission, we found that a lower BMI, lower GFR, longer hospitalization duration, new-onset AF in the hospital and the restrictive filling pattern on echocardiography were factors that significantly increased in-hospital mortality. Being on ACE-I/ARB drugs before admission was protective against in-hospital mortality. These factors were all in accordance with the literature; however, one cannot conclude a definite association because of the small number of patients enrolled in our trial (15-17). We believe the independent association of in-hospital mortality and new-onset AF should be considered since it was detected in a very select patient population. Of course, the data needs to be further verified with larger randomized studies.

Study Limitations

A major limitation of our study is that it is a retrospective analysis with a small number of patients from a single center. Our results represent the data of hospital follow-up 119 patients who were selectively enrolled and admitted with decompensation of HFrEF. We believe that we included valuable data for further research; however, our results and conclusions should be interpreted with caution.

Conclusion

Our data suggest that patients with new-onset AF and those with longer hospitalization durations had higher in-hospital mortality rates. We believe that this data should reinforce the value of optimal HF treatment according to guidelines, not only to slow disease progression but also to reduce the risk of new-onset AF. New-onset AF in a HFrEF patient should alert the physician to the need of heightened clinical observation and to consider more intensified HF treatment.

Ethics

Ethics Committee Approval: This study was approved by Ankara University School of Medicine, Clinical Researches Ethics Committee (date: 10.10.2016, decision no: 15-756-16).

Informed Consent: Retrospective study.

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Authorship Contributions

Surgical and Medical Practices: N.Ö., Concept: N.Ö., S.G., Design: N.Ö., S.G., Data Collection or Processing: N.Ö., Analysis or Interpretation: N.Ö., S.G., Literature Search: N.Ö., Writing: N.Ö., S.G.

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