ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

The Effect of the Practical Treatments for Acute Heart Failure on Mortality: A Real-World Study

Akut Kalp Yetmezliğinde Uygulanan Tedavilerin Mortalite Üzerine Etkisi: Bir Gerçek Dünya Çalışması

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ABSTRACT

Aim: *The mortality of chronic systolic heart failure has been decreased thanks to state-of-the-art therapy. However, the mortality rate is still high in acute heart failure (AHF). Our study was planned to investigate the mortality rates and predictors of mortality in AHF.*

Material and Method: *A single-center retrospective study was conducted on 805 patients hospitalized due to AHF between March 2009 and June 2013. The patients were separated into two main groups: the decompensated heart failure group (DHF), which comprised the patients with signs of right heart failure with or without pulmonary edema (722 patients – 89.7%), and the acute pulmonary edema group (PE) presenting only with pulmonary edema (83 patients – 10.3%). The two groups were compared for the patient-related variables. The survival analysis of the groups based on the etiology was performed. Finally, the independent predictors for 2-year mortality in AHF were investigated.*

Results: *The 2-year mortality rate was higher in DHF than in PE (51.4% vs. 31.6% p<0.001). The mortality rates of ischemic cardiomyopathy, nonischemic cardiomyopathy, and heart failure with preserved ejection fraction (HFpEF) were 52.8%, 39.6%, and 47.3%, respectively (p=0.389). Advanced age, previous cerebrovascular diseases, anemia, hyponatremia, hypoalbuminemia, lower left ventricular ejection fraction (LVEF), and lower systolic blood pressure predicted increased 2-year mortality independently. In contrast, usage of beta-blockers during hospitalization predicted reduced 2year mortality independently.*

Conclusion: *Mortality rate was similar between different heart failure types. Various laboratory and clinical parameters predict mortality, whereas beta-blockers and ACE inhibitors reduce mortality.*

Key words: *mortality; acute heart failure; ACE inhibitors; beta blockers*

ÖZET

Amaç: *Güncel tedavi uygulamalarıyla kronik sistolik kalp yetmezliği mortalitesinde azalma sağlanmıştır. Ancak akut kalp yetmezliğinde (AKY) mortalite hala yüksektir. Bizim çalışmamızda AKY hastalarında mortalite oranları ve mortalitenin ön gördürücülerinin neler olduğu araştırılmıştır.*

Materyal ve Metot: *Çalışmamız Mart 2009 ve Haziran 2013 tarihleri arasında AKY tansıyla yatırılan 805 hastayı içeren tek merkezli retrospektif bir çalışmadır. Çalışmadaki hastalar iki ana gruba ayrıldı: pulmoner ödemin eşlik ettiği ya da etmediği sağ kalp yetmezliği kliniği ile başvuran hastaları içeren (722 hasta – %89,7) dekompanze kalp yermezliği (DKY) grubu, sadece pumoner ödem klinği ile başvuran hastaları içeren (83 hasta – %10,3) pulmoner ödem grubu (PÖ). İki grup arasında hastalara ait değişkenler istatiksel olarak karşılaştırıldı. Etiyolojiye göre ayrılmış hasta gruplarının sağ kalım analizi yapıldı. En sonda da AKY de 2 yıllık mortaliteyi öngören bağımsız faktörler araştırıldı.*

Bulgular: *İki yıllık mortalite DKY grubunda PÖ grubundan daha fazlaydı (%51,4 ve %31,6 p<0,001). İskemik kardiyomiyopati, non iskemik kardiyomiyopati, korunmuş ejeksiyonlu kalp yetmezliği (kEFKY) hastalarında mortalite oranları sırasıyla %52,8, %39,6 ve %47,3 idi. (p: 0,389). İleri yaş, serebrovasküler olay öyküsü, anemi, hiponatremi, hipoalbuminemi, düşük sol ventrikül ejeksiyon fraksiyonu (SVEF), düşük sistolik kan basıncı 2 yıllık artmış mortaliteyi öngören bağımsız faktörler olarak bulunurken hastane yatışında beta bloker kullanımı mortaliteyi azaltan bağımsız faktör olarak bulundu.*

Sonuç: *Mortalite oranları farklı kalp yetmezliği gruplarında benzer saptandı. Çeşitli klinik ve laboratuvar parametreleri AKY de mortaliteyi artıran öngördürücüler olurken beta bloker ve anjiyotensin dönüştürücü enzim (ADE) inhibitör kullanımı mortaliteyi azaltan öngördürücüler oldu.*

Anahtar kelimeler: *mortalite; akut kalp yetmezliği; ACE inhibitörü; beta bloker*

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Introduction

Heart failure (HF) is a phenomenon that occurs as a result of deterioration in cardiac filling or pumping. The practical guidelines state HF as a clinical syndrome including cardinal symptoms and signs (e.g., breath shortness, ankle edema fatigue, elevated jugular venous pressure, pulmonary crackles, S3 heart sound) due to structural or functional heart disease[1-3].

The current guidelines prefer a classification for HF based on left ventricle ejection fraction (LVEF): heart failure with preserved ejection fraction (HFpEF), defined by an LVEF ≥50%, heart failure with reduced ejection fraction (HFrEF) if the LVEF is <40%, and heart failure with mid-range ejection fraction (HFmrEF) if the LVEF is 40–49%[2].

HF is one of the main reasons for mortality in the world. Increased lifetime due to the administration of advanced treatments in cardiovascular disease has increased the prevalence of HF and healthcare costs [2,4].

The mortality benefit of medical therapy in HFrEF has been shown in numerous studies. In contrast, no treatment has been found to ameliorate the mortality in HFpEF[5].

Acute heart failure (AHF) is the sudden occurrence or worsening of HF's signs and symptoms.AHF can be diagnosed for the first time (de novo) or manifest as chronic heart failure decompensation. It can be fatal if not treated immediately[2].

Determining the etiology and predisposing factors of acute heart failure rapidly-it has been mentioned in the 2016 ESC heart failure guideline widely- is essential for the proper treatment[2]. Medication for acute heart failure can also be challenging because there are no sufficient data for the effects of the medications which are proven beneficial for systolic heart failure (angiotensin-converting enzyme inhibitors, beta-blockers, angiotensin receptor blockers, ivabradine mineralocorticoid receptor antagonists, etc.)[6-10].

This study aimed to determine the mortality rates of patients hospitalized due to AHF and the variables that affect mortality in AHF.

Materials and Method

The study was a retrospective study conducted in a single center (Izmir Katip Celebi University Ataturk Training and Research Hospital). One thousand one hundred fifty-two patients hospitalized with a diagnosis of AHF between March 2010 and June 2013 were recorded. AHF was defined as the sudden occurrence or aggravating of HF's signs and symptoms. The patients' clinical and laboratory characteristics were obtained from the "hospital information management system."The exclusion criteria were hospitalization due to a non-cardiovascular disease (diabetic coma, acute renal failure, etc.), 'dry patients'(with no congestion/ pulmonary edema), insufficient hospital information management system data, and discharge on the same day. After considering these criteria, 805 patients were eligible for this study. The patients were separated into two main groups based on clinical presentation: the decompensated heart failure group(DHF), which comprised the patients with signs of right heart failure with or without pulmonary edema (722 patients -89.7%), and the acute pulmonary edema group(PE) presenting only with pulmonary edema (83 patients -% 10.3). İzmir Katip Çelebi University Ethics Committee approved the study. Non-invasive Clinical Tria for this study with the decision number 212, dated 11.11.2013.

Statistical Analysis

SPSS 21 (IBM) statistics program was used for the statistical analysis. Since the variables were shown to distribute normally by the Shapiro-Wilk test, the categorical and continuous variables of the patients were compared across the dichotomous dependent variables (DHF and PE groups) using chi-square, Fischer exact, one-way ANOVA as appropriate. To identify the independent predictors for two year mortality in AHF, a multivariate Cox proportional-hazards regression model analysis was conducted among the variables of which the p-value was shown <0.05 using univariate cox regression analysis. The variables with a p-value of below 0.05 in that model were accepted as independent predictors.

Results

20.2% of the 805 patients (51.4% men with a mean age of 72 + 12 years) had no previous history of HF (de novo AHF). Clinical and demographic findings of the patients are shown in Table 1.

Hypertension, hyperlipidemia, and chronic renal failure were more prevalent in PE (p:<0.05), whereas history of atrial fibrillation was more prevalent in DHF (p<0.05). On admission, the mean heart rate and systolic/diastolic blood pressure were higher in PE

Table 1. *Clinical and Demographic findings on admission*

Variables	Decompensated heart failure (n: 722)	Acute pulmonary edema (n: 83)	p
Age Mean ± SD	71.53±12.28	72.00±12.17	0.739
Male n (%)	378 (52.4%)	36 (43.4%)	0.121
LVEF% Mean ± SD	38.67±15.23	45.90±12.40	**<0.001**
De novo Heart Failure n (%)	141 (19.5%)	21 (26.5%)	0.134
Coronary artery disease n (%)	341 (47.2%)	42 (50.6%)	0.560
Thyroid disease n (%)	109 (15.1%)	6 (7.2%)	0.052
Hypertension n (%)	393 (54.4%)	58 (69.9%)	**0.007**
Diabetes Mellitus n (%)	307 (42.5%)	44 (53.0%)	0.068
Hyperlipidemia n (%)	133 (18.4%)	27 (32.5%)	**0.002**
Severe valvular heart disease n (%)	84 (11.6%)	5 (6.0%)	0.123
Cerebrovascular disease n (%)	54 (7.5%)	7 (8.4%)	0.756
ICD n (%)	101 (14.0%)	9 (11.3%)	0.429
CRT n (%)	5 (0.7%)	0 (0.0%)	0.447
Atrial fibrillation n (%)	251 (34.8%)	16 (19.3%)	**0.005**
COPD n (%)	213 (29.5%)	22 (26.5%)	0.570
Chronic renal failure* n (%)	286 (39.6%)	44 (53.0%)	**0.019**
Smoking n (%)	187 (25.9%)	23 (27.7%)	0.722
Class 3 Obesity** n (%)	35 (4.7%)	5 (7.2%)	0.317
Valvular heart surgery n (%)	37 (5.1%)	3 (3.6%)	0.789
ACE inhibitors/ARB n (%) (n: 678)	253 (41.1%)	27 (43.5%)	0.706
Beta blockers n (%) (n: 678)	278 (45.1%)	32 (51.6%)	0.329
MRAs n (%) (n: 678)	193 (31.3%)	9 (14.5%)	**0.006**
Furosemid n (%) (n: 678)	345 (56.0%)	20 (32.3%)	**<0.001**

ACE: Angiotensin-converting enzyme, ARB: Angiotensin II receptor blocker, COPD: chronic obstructive pulmonary disease, CRT: Cardiac resynchronization therapy, ICD: Implantable cardioverter defibrillator, LVEF: left ventricular ejection fraction, MRA: Mineralocorticoid receptor antagonist
* glomerular filtration rate less than 60 ml/min/1.73 m^2 for at least three months
** body mass index more than 40

(p:<0.05). The mean left ventricular ejection fraction (LVEF) was significantly lower in DHF (38.67% vs. 45.90% p<0.001). The rate of hyponatremia (sodium <135 meq/l) was higher among DHF (p<0.05). The clinical variables and biomarkers are shown in Table 2.

The patients were also separated into the groups based on the mechanism of HF: ischemic cardiomyopathy(ICM -32.5%), non-ischemic dilated cardiomyopathy (NICM-4.4%), valvular heart failure (15.6%), high output heart failure (2.9%) and heart failure with preserved ejection fraction-HFpEF(28.1%). The etiology for 16.6% of the patients could not be identified.

The acute comorbidities on admission were as follows: infection (20.2%), stage 3 hypertension (16.7%), acute coronary syndrome (12.2%), and arrhythmia (38.2%).132 (%16,3) of the patients underwent coronary angiography due to suspicion of coronary ischemia. 23 of those patients (2.8%) underwent percutaneous transluminal coronary angioplasty (PTCA) following angiogram. Two patients died during PTCA. The most common arrhythmia observed in the study was atrial fibrillation (AF) (33.2%). Seventy-eight of the patients with AF (9.6%) were newly diagnosed. Only five patients (0.6%) were diagnosed with ventricular tachycardia.

The medication history could be recorded for 678 patients (616 for DHF and 62 for PE). Mineralocorticoid receptor antagonist (MRA) and furosemide usage were observed more commonly in DHF (p<0.05). Angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARB) and digoxin were ordered more commonly in DHF at hospitalization (p<0.05). Prescription rates of ace inh/arb,

Table 2. *Examination and laboratory findings on admission*

Variables	Decompensated heart failure (n: 722)	Acute pulmonary edema (n: 83)	p
Systolic blood pressure (mmhg mean ± SD)	129.2±33.3	184.4±56.8	**<0.001**
Diastolic blood pressure (mmhg mean ± SD)	74.6±18.4	104.2±25.6	**<0.001**
Heart rate bpm, mean ± SD)	92±33.6	103±42.4	**0.001**
Saturation (mean% ± SD)	86.83±14.78	80.12±16.91	**0.008**
Sodium<135 mEq/l n (%)	483 (66.9%)	45 (54.2%)	**0.021**
Potasium >5.5 mmol/l n (%)	70 (9.7%)	4 (4.9%)	0.145
Albumine<3.5 gr/dl n (%)	183 (25.3%)	14 (16.9%)	0.089
FBG >200 mg/dl n (%)	117 (16.2%)	17 (20.5%)	0.322
Hemoglobine<12 g/dl n (%)	246 (34.1%)	28 (33.7%)	0.951
ACE inhibitors/ARB n (%)	431 (59.7%)	63 (75.9%)	**0.004**
Beta blockers n	413 (57.2%)	52 (62.7%)	0.341
MRAs n (%)	203 (28.1%)	26 (31.3%)	0.539
Digoxin n (%)	198 (27.4%)	11 (13.3%)	**0.005**

ACE: Angiotensin-converting enzyme, ARB: Angiotensin II receptor blocker, FBG: Fasting blood glucose, MRA: Mineralocorticoid receptor antagonist.

Table 3. *Mortality rates for subgroups of acute heart failure*

	In hospital mortality	1-month mortality	6-month mortality	12-month mortality	24-month mortality
Ischemic cardiomyopathy	20 (5.5%)	51 (14.9%)	103 (30.0%)	143 (41.7%)	181 (52.8%)
Nonischemic cardiomyopathy	1 (2.0%)	3 (6.3%)	8 (16.7%)	13 (27.1%)	19 (39.6%)
SevereValvular heart disease	5 (4.1%)	19 (16.1%)	43 (36.7%)	49 (41.5%)	57 (48.3%)
High-output heart failure	0 (0.0%)	2 (8.7%)	4 (17.4%)	8 (34.8%)	10 (43.5%)
HFpEF	5 (2.0%)	25 (10.4%)	61 (25.3%)	75 (31.1%)	114 (47.3%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100%)

HFpEF: Heart failure with a preserved ejection fraction.

beta-blocker, and MRA at discharge were 49.1%, 49.9%, and 33.6%, respectively. There were no statistically significant differences between the medications prescribed at discharge rates except that MRA was prescribed more commonly in DHF (34.8% vs. 10.8%, p<0,01).

The in-hospital mortality, 1- year mortality, and 2-year mortality data of the groups separated by the etiology were shown in Table 3. The 2-year mortality was 52.8% among the ICM patients, whereas it was 39.6% among the NICM group. There were no statistically significant differences in the 2 -year mortality between the groups (p=0,389). The survival rates of groups are shown in Fig. 1. According to the clinical status, the 2-year mortality rate was higher in DHF than in PE (51.4% vs. 31.6% p<0,001). Moreover, the two-year mortality rate was lower in de novo AHF than in acutely decompensated chronic HF (41.9% vs. 51.2% p:0,039).

The Cox proportional-hazards model revealed that advanced age, previous cerebrovascular diseases, anemia, hyponatremia, hypoalbuminemia, lower LVEF, and lower systolic blood pressure were independent predictors for increased risk of 2-year mortality. In contrast, usage of beta-blockers at hospitalization and ACE inhibitors at discharge were predictors for improved two-year mortality (Table 4).

Discussion

Our study showed that the in-hospital, one-year, and two-year mortality rates in AHF patients were 3.8%, 35.7%, and approximately 50%, respectively. The in-hospital and 1-year mortality rates were comparable to those found in the previous large studies[11-13]. In the Cox proportional-hazards model, advanced age, lower LVEF, cerebrovascular event, low systolic blood pressure, hypoalbuminemia, and hyponatremia were

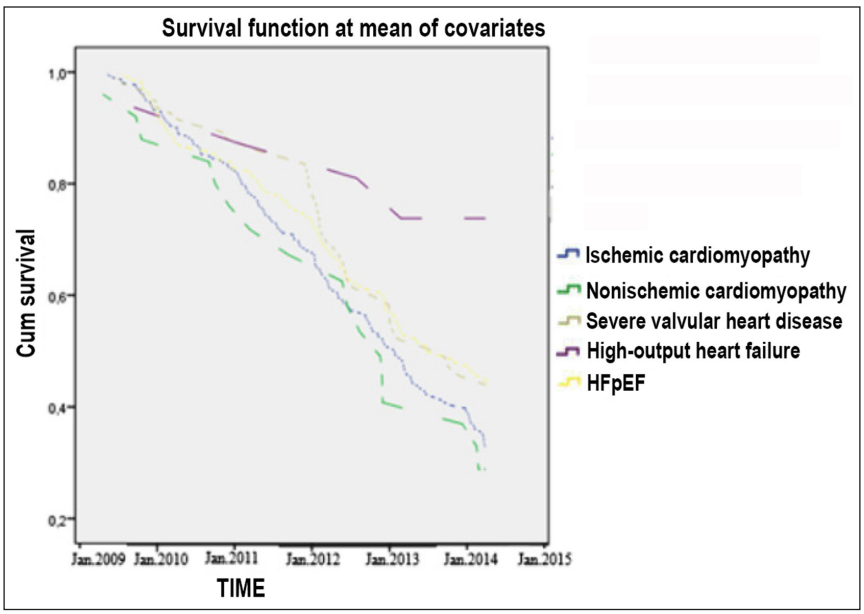

Figure 1. *Survival analysis of acute heart failure patients.*

Table 4. *Independent predictors of 2-year mortality in acute heart failure*

Univariate analysis				Multivariate analysis			
Variables	HR	95% CI	P value	Variables	HR	95% CI	P value
Male	0.866	0.653–1.149	0.319	Age	1.037	1.021–1.053	<0.001
Age	1.036	1.023–1.049	<0.001	LVEF	0.981	0.968–0.993	0.003
LVEF	0.965	0.937–0.977	0.005	De novo HF	1.105	0.708–1.724	0.661
De novo HF	0.978	0.959–0.997	0.006	CVD	2.130	1.101–4.121	0.025
CAD	0.909	0.685–1.205	0.507	Systolic BP	0.988	0.980–0.996	0.003
CVD	2.236	1.285–3.893	0.004	Diastolic BP	0.999	0.983–1.014	0.869
Diabetes	1.167	0.878–1.552	0.287	Hyperlipidemia	0.780	0.512–1.189	0.249
Systolic BP	0.988	0.983–0.993	<0.001	CRF	1.033	0.988–1.104	0.352
Diastolic BP	0.979	0.970–0.988	<0.001	Sodium<135 mEq/l	1.351	1.124–1.629	<0.001
Hyperlipidemia	0.629	0.442–0.897	0.010	Albumine<3.5 gr/dl	1.629	1.062–2.500	0.025
Thyroid disease	0.911	0.609–1.362	0.649	Hemoglobine<12 g/dl	1.102	0.951–1.257	0.574
Atrial fibrillation	0.951	0.706–1280	0.739	Beta blocker in hospital	0.532	0.334–0.848	0.008
COPD	0.770	0.564–1.050	0.099	ACE inh/ARB in hospital	0.971	0.632–1.490	0.892
CRF	1.259	1.045–1.353	<0.001	ACEinh/ARBatdischarge	0.774	0.510–0.984	0.015
Beta blockers usage	1.097	0.757–1.589	0.624	Beta blocker at discharge	0.950	0.604–1.495	0.826
ACEinh/ARB usage	1.269	0.879–1.831	0.203	ICD	0.640	0.202–2.024	0.447
HR on admission	0.997	0.991–1.004	0.402	DHF	0.888	0.448–1.761	0.733
Sodium<135 mEq/l	1.762	1.303–2.384	<0.001				
Albumine<3.5 gr/dl	2.577	1.821–3.647	<0.001				
Hemoglobine<12 g/dl	2.168	1.596–2.946	<0.001				
Beta blocker in hospital	0.610	0.457–0.814	0.001				
ACE inh/ARB in hospital	0.526	0.471–0.657	0.002				
MRA in hospital	0.812	0.593–1.113	0.195				
ACE inh/ARBatdischarge	0.576	0.433–0.766	<0.001				
Beta blocker at discharge	0.475	0.357–0.633	<0.001				
MRA at discharge	1.089	0.808–1.468	0.575				
ICD	0.640	0.423–0.969	0.035				
DHF	2.281	1.388–3.750	0.001				

ACE: Angiotensin-converting enzyme, ARB: Angiotensin receptor blocker, BP: Blood pressure, CAD: Coronary artery disease, CHF: Chronic renal failure, glomerular filtration rate less than 60 ml/min/1.73 m2 for at least three months, COPD: Chronic obstructive pulmonary disease CVD: Cerebrovascular disease, DHF: Decompensated heart failure, HR: Heart rate, HF: Heart failure, ICD: Implantable cardioverter-defibrillator, LVEF: left ventricular ejection fraction, MRA: mineralocorticoid receptor antagonist.

independent predictors that increased two year mortality. In contrast, the usage of beta-blockers during hospitalization and ACE inhibitors at discharge were determined as predictors that decreased two year mortality.

AHEAD Main, a study conducted to determine long-term survival rates in AHF, showed that one-year and three-year survival rates of patients were 79.7% and 64.5%, respectively[11]. In the EFICA study, 1-year mortality among AHF was 46.5%[12]. In ADHERE trial, the in-hospital mortality of the 65.180 patients with AHF was 4.1%, whereas the one-year mortality was 36%[13]. ALARM HF revealed that the overall hospital death rate was 12% among AHF[14]. In both OPTİMIZE trial and the ESC-HF Pilot trial, in-hospital mortality was reported in 3.8% of AHF patients[15,16]. Our study's hospital mortality rate was similar to ADHERE, OPTİMIZE, and ESC-HF Pilot but lower than ALARM HF. The higher in-hospital mortality rate in ALARM HF was attributed to the severity of ALARM patients. (the incidence of cardiogenic shock was 11.7%)[14]. One year mortality rate of our study was comparable to ADHERE, higher than AHEAD Main, and lower than the EFICA study. Those differences in the rates were considered to be driven by many factors, including the patients' heterogeneity and difference in the design of the studies.

There was no statistically significant difference between the 2-year mortality rates of ICM and NICM. The clinical studies investigating the difference in prognosis between ICM and NICM have produced conflicting results[17-19].

Harjola et al.showed that age, low plasma sodium, previous myocardial infarction, and creatinine level were independent predictors for one-year mortality in AHF patients[20]. Similarly, hyponatremia and older age were independent predictors in our study. Previous large studies also revealed that hypoalbuminemia, hyponatremia, lower systolic blood pressure, and lower LVEF were independently associated with mortality in heart failure[21-25]. Similar to our study, the meta-analysis of Prins et al. revealed that non-withdrawal of beta-blockers in AHF was an independent predictor for increased survival time[26]. The neutral effect of MRA on mortality was primarily attributed to the etiologic heterogeneity in AHF.

The study was designed as a retrospective study and conducted in a single center. Due to the study's design, patient compliance with medical treatment after discharge was unknown. The medications other than ACE inhibitors /ARB, beta-blockers, and MRA were not assessed for effects on mortality.

Conclusion

In our study, mortality rates in AHF were similar to those in the large-scale studies. While hypoalbuminemia, hyponatremia, lower systolic blood pressure, and lower LVEF on admission increased 2-years mortality, beta-blocker use during hospitalization and ACE inhibitors administration at discharge decreased two years of mortality.

Acknowledgments

We have not received substantial contributions from non-authors.

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