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The Effect of Early Diuretic Treatment on Clinical Outcomes in Patients with Acute Heart Failure: Door to Diuretic

Akut Kalp Yetmezliği Hastalarında Erken Diüretik Uygulamasının Klinik Sonlanımlara Etkisi: Kapı Diüretik Zamanı

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Abstract

Objective: It was aimed to investigate the effect of early diuretic treatment on hospitalization and short-term mortality in patients with acute heart failure.

Method: Our study was carried out as a retrospective, single-centered, observational study in the department of emergency a tertiary training and research hospital. The study population was the patients presenting with signs and symptoms of acute heart failure. The primary outcome was all-cause 30-day mortality and hospitalization. Univariant tests and ROC analysis were used for analysis.

Results: A total of 325 patients were included. The median age of the patients was 76.0 years (interquartile range 69.0-83.0). The mortality rate of our study population was %14.4 (47). Systolic blood pressure and diastolic blood pressure were significantly higher in the survivor group (p=0.018, 0.033, respectively). Age, troponin-I, and pro-brain natriuretic peptide were significantly higher in the non-survivor group (p<0.001, <0.001, <0.001, respectively). For hospitalization, the area under the curve for the high door to diuretic time was 0.570, the cut-off value was 99 minutes, and the odds ratio was 1.75 (95% confidence interval: 1.09-2.82).

Conclusion: Early initiation of diuretic treatment has no effect on short-term mortality. However, delayed initiation of diuretic treatment may affect hospitalization rates. According to our results, early initiation of diuretic treatment may reduce hospitalization rates.

Keywords: Acute disease, diuretics, emergency service, heart failure, time-to-treatment

Öz

Amaç: Akut kalp yetmezliği hastalarında erken diüretik uygulamasının hastane yatışına ve kısa dönem mortaliteye etkisini araştırmak amaçlanmıştır.

Yöntem: Çalışmamız retrospektif, tek merkezli, gözlemsel çalışma olarak üçüncü basamak eğitim araştırma hastanesinin acil servisinde gerçekleştirildi. Çalışma popülasyonu, akut kalp yetmezliği belirtileri ve semptomları ile başvuran hastalardı. Demografi, yaşamsal parametreler ve laboratuvar parametreleri kaydedildi. Birincil sonlanım tüm nedenler bağlı 30 günlük mortalite ve hastane yatışıydı. Analiz için tek değişkenli testler ve ROC kullanıldı.

Bulgular: Çalışmaya 325 hasta dahil edildi. Hastaların ortanca yaşı 76,0 (çeyrekler arası aralık 69,0-83,0) idi. Çalışma popülasyonumuzun ölüm oranı %12 idi. Sistolik kan basıncı ve diyastolik kan basıncı yaşayanlarda anlamlı yüksekti (p=0,018, 0,033). Yaş, troponin I ve pro-beyin natriüretik peptidi ölenlerde anlamlı yüksekti (p-değeri sırası ile, <0,001 ve <0,001, <0,001). Hastane yatışı için yüksek kapı diüretik zamanı eğri altında kalan alan 0,570, kesme değeri 99 dakika ve olasılık oranı 1,75 (%95 güven aralığı: 1,09-2,82) olarak hesaplandı.

Sonuç: Diüretik tedavinin erken başlanmasının kısa dönem mortaliteye etkisi yoktur. Bununla birlikte geciken diüretik tedavisi hastane yatış oranlarını etkileyebilmektedir. Sonuçlarımıza göre erken diüretik tedavi başlanması hastaneye yatış oranlarını azaltabilir.

Anahtar kelimeler: Acil servis, akut hastalık, diüretikler, kalp yetmezliği, tedaviye kalan süre

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Introduction

Heart failure (HF) is a clinical syndrome that includes complex diseases. Its incidence is expected to increase in the coming years (1). Advanced age is one of the risk factors (2). The most common causes are ischemic heart disease, valvular diseases and hypertension. It is estimated that there are more than 64 million patients with HF worldwide (3). The prognosis of HF is not promising (4). The mortality rate in the first five years approaches 50% (5). Acute heart failure (AHF) is the rapid onset or sudden deterioration of HF symptoms. It is a life-threatening condition with high morbidity and mortality rates. Emergency departments are where the treatment of AHF begins. It is recommended to use international guidelines in the treatment of these patients (6). Effective treatment of symptomatic HF patients also reduces clinical outcomes, quality of life and health expenditures (7).

Despite the development of new medical treatments for many diseases, the management of AHF has not changed significantly for decades. Most drug trials did not show a positive prognostic effect (8). Intravenous (IV) diuretics treatment is the main therapy in the management of AHF. A significant relationship between IV furosemide and in-hospital mortality was demonstrated in studies (9). Door to diuretic treatment in AHF patients is a controversial issue to researchers (10). In this study, it was aimed to evaluate the effect of early diuretic treatment short-term mortality and hospitalization in AHF patients in the emergency department.

Materials and Methods

This was a retrospective, single-centered and observational study. It was carried out in the 655-bed tertiary care Clinic of Emergency University of Health Sciences Turkey, Ümraniye Training and Research Hospital.

Our study population included patients who had signs and symptoms of AHF between January 1, 2019, and January 1, 2020. These symptoms and signs were dyspnea, effort dyspnea, chest pain, fatigue, weakness, edema in the lower extremities, orthopnea, and intra-abdominal ascites. The patients were diagnosed with HF as a result of the evaluation made by the emergency cardiologist or there had been definitive diagnosis of HF within the last 6 months. All patients had a B-type natriuretic peptide higher than normal values. Patients under 18 years of age and those with missing data or unknown mortality status were excluded.

Patient data were scanned from the hospital computer-based data system. Demographic characteristics, comorbidities, laboratory parameters, systolic and diastolic blood pressure, oxygen saturation and pulse values, and hospital stay were recorded. From laboratory parameters; white blood cell count, neutrophil count, lymphocyte count, hemoglobin, hematocrit, platelet count, potassium, mean platelet volume, sodium, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, C-reactive protein/albumin ratio, blood urea nitrogen/albumin ratio, troponin and pro-BNP recorded. All-cause mortality within 30 days of the patients was recorded using the national death notification system.

Approval for the study was obtained from the Local Ethics Committee of University of Health Sciences Turkey, Ümraniye Training and Research Hospital (no: 426, date: 14/01/2021).

Statistical Analysis

The Jamovi (Version 1.6.21.0; The Jamovi Project, 2020; R Core Team, 2019) was used for statistical analyses. The Shapiro-Wilk test was used in the analysis of normality of data. Categorical data were presented as numbers (%) and compared with the chi-square test. Quantitative variables were presented as median and interquartile range (IQR) (25^{th}-75^{th} percentile) values and then compared for normality of distribution for the two groups using the Mann-Whitney U test or Student's t-test. Receiver operating characteristic (ROC) curves were used to determine the predictive power of door diuretic time in predicting hospitalization, and the results were reported as area under the curve (AUC) values. The optimal cut-off value for the parameters with the highest sensitivity and specificity was determined using the Youden index. Odds ratios and 95% confidence intervals of the groups were calculated according to the cut-off value. For p-values, values less than 0.05 were considered statistically significant.

Results

During the study period, a total of 426 patients were recorded in the emergency department with signs and symptoms of AHF. The excluded were 101 patients. As a result, 325 patients were ultimately included.

The median age of the patients was 76.0 (IQR 69.0-83.0). Male were 155 (47.7%). All causes mortality within 30 days were 47 (14.4%). The number of patients who were hospitalized was 138 (42%). The basic characteristics of the survivors and non-survivors are shown in Table 1. Systolic blood

pressure and diastolic blood pressure were significantly higher in the survivor group (p=0.018, 0.033). Age, troponin I, and pro-BNP were significantly higher in non-survivor group (p<0.001, <0.001, <0.001, respectively). There was no significant relationship between door to diuretic treatment and short-term mortality (p=0.539). Hemoglobin and hematocrits values were significantly higher in discharged group (p=0.016, 0.012 respectively). Mortality rate was found to be significantly higher in hospitalized patients 31 (22.5%) (p=0.001). Door to diuretic treatment in hospitalized patients was 62.5 (30.0-149.2) minutes. This value was significantly higher than discharged group 40.0 (22.0-111.0) (p=0.033). The left ventricular ejection fraction (LVEF) was higher in hospitalized than in discharged (p=0.013).

Table 1. Baseline characteristics of the study population and comparison between survivor and non-survivors groups

Parameters	Total n=325	Survivors n=278 (85.6%)	Non- survivors n=47 (14.4%)	p
	n (%)/median (25.-75. percentage)	n (%)/median (25.-75. percentage)	n (%)/median (25.-75. percentage)	
Age	76.0 (69.0-83.0)	76.0 (68.2-82.0)	82.0 (75.5-87.0)	<0.001
<65	52 (16.0)	51 (18.3)	1 (2.1)	0.01
≥65	273 (84.0)	227 (81.7)	46 (97.9)	
Sex				
Female (%)	28 (47.5)	21 (42.9)	7 (70.0)	0.223
Male (%)	31 (52.5)	28 (57.1)	3 (30.0)	
Comorbidities				
Chronic obstructive pulmonary disease (%)	77 (23.7)	67 (24.1)	10 (21.3)	0.814
Hypertension (%)	141 (43.4)	123 (44.2)	18 (38.3)	0.547
Diabetes mellitus (%)	110 (33.8)	97 (34.9)	13 (27.7)	0.422
Coronary artery disease (%)	70 (21.5)	62 (22.3)	8 (17.0)	0.533
Heart failure disease (%)	193 (59.4)	167 (60.1)	26 (55.3)	0.651
Chronic kidney disease (%)	68 (20.9)	59 (21.2)	9 (19.1)	0.897
Malignity (%)	10 (3.1)	8 (2.9)	2 (4.3)	0.961
Diuretic use (%)	151 (46.5)	132 (47.5)	19 (40.4)	0.460
Vital parameters				
Systolic blood pressure (mm/hg)	142.5 (122.0-170.0)	144.0 (124.0-170.0)	131.0 (110.0-150.0)	0.018
Diastolic blood pressure (mm/hg)	80.0 (68.0-95.0)	80.0 (70.0-95.5)	70.0 (65.0-90.0)	0.033
Oxygen saturation (%)	92.0 (85.2-95.0)	92.0 (86.0-95.0)	92.0 (85.0-94.0)	0.543
Laboratory parameters				
White blood cell count (10^3/μL)	9.2 (7.0-12.2)	9.1 (6.9-12.0)	10.1 (7.7-13.6)	0.142
Neutrophil count (10^3/μL)	6.8 (5.0-9.0)	6.7 (4.9-8.8)	7.4 (5.2-10.9)	0.092
Lymphocyte count (10^3/μL)	1.4 (0.9-2.1)	1.4 (1.0-2.1)	1.3 (0.8-2.4)	0.52
Hemoglobin (g/dL)	11.1 (9.8-12.6)	11.1 (9.8-12.6)	11.0 (9.9-12.6)	0.865
Hematocrit (%)	35.5 (31.2-40.0)	35.5 (31.2-40.0)	35.1 (31.1-39.8)	0.83
Mean platelet volume (fL)	88.2 (82.6-92.2)	88.1 (82.6-91.8)	88.5 (82.6-92.8)	0.553
Blood urea nitrogen (mg/dL)	64.2 (47.1-101.1)	62.1 (47.1-94.2)	96.3 (59.9-127.3)	0.001
C-reactive protein (mg/dL)	1.8 (0.5-4.7)	1.6 (0.5-4.4)	3.2 (0.7-9.5)	0.021
Albumin (g/dL)	3.5 (3.2-3.7)	3.5 (3.2-3.7)	3.5 (3.1-3.8)	0.923
Creatinine (mg/dL)	1.3 (1.0-1.9)	1.6 (1.1- 2.5)	1.3 (1.0-2.0)	0.03
Sodium (mEq/L)	138.0 (135.0-140.0)	138.0 (136.0-140.0)	137.5 (135.0-140.0)	0.295
Potassium (mmol/L)	4.8 (4.4-5.3)	4.8 (4.5-5.3)	4.7 (4.3-5.4)	0.756
Troponin I (μg/L)	0.0 (0.0-0.1)	0.0 (0.0-0.1)	0.1 (0.0-0.2)	<0.001
Brain natriuretic peptide (pg/mL)	1170.8 (760.3-2027.5)	1078.2 (732.0-1821.5)	1858.7 (1376.1-2844.6)	<0.001
Left ventricular ejection fraction (%)	45.0 (30.0-55.0)	45.0 (30.0-55.0)	40.0 (30.0-50.0)	0.567
Door to treatment (min.)	46.0 (24.0-120.0)	48.0 (23.0-122.2)	40.0 (27.0-117.5)	0.539

Comparison of all parameters between hospitalized and discharged is given in Table 2. According to the ROC analysis result of door to diuretic treatment predicting hospitalization, AUC was 0.570, cut-off was 99 minutes, Sensitivity was 37.48%, specificity was 74.33%, positive likelihood ratio was 52%, and negative likelihood ratio was 61.78%. Door to diuretic treatment cut-off values and odds ratios of mortality and hospitalization are given in Table 3. A model consisting of door to treatment duration, LVEF, C-reactive protein, creatinine, brain natriuretic peptide and albumin can predict hospitalization with 85% specificity and 54% sensitivity. Logistic regression analysis

Table 2. Comparison of all parameters between hospitalized and discharged patients

Parameters	Discharged n=187 (58%)	Hospitalized n=138 (42%)	p
	n (%)/median (25.-75. percentage)	n (%)/median (25.-75 percentage)	
Age	76.0 (69.0-82.0)	77.0 (69.0-85.0)	0.191
<65	30 (16.0)	22 (15.9)	0.999
≥65	157 (84.0)	116 (84.1)	
Sex			
Female (%)	95 (50.8)	75 (54.3)	0.603
Male (%)	92 (49.2)	63 (45.7)	
Comorbidities			
Chronic obstructive pulmonary disease (%)	48 (25.7)	29 (21.0)	0.399
Hypertension (%)	74 (39.6)	67 (48.6)	0.133
Diabetes mellitus (%)	55 (29.4)	55 (39.9)	0.065
Coronary artery disease (%)	37 (19.8)	33 (23.9)	0.448
Heart failure disease (%)	104 (55.6)	89 (64.5)	0.135
Chronic kidney disease (%)	32 (17.1)	36 (26.1)	0.068
Malignity (%)	6 (3.2)	4 (2.9)	1.000
Vital parameters			
Systolic blood pressure (mm/hg)	140.0 (123.8-164.2)	145.0 (120.0-171.0)	0.502
Diastolic blood pressure (mm/hg)	80.0 (70.0-95.0)	78.0 (65.0-95.2)	0.328
Oxygen saturation (%)	92.0 (87.0-95.0)	90.0 (85.0-95.0)	0.191
Laboratory parameters			
White blood cell count (10^3/μL)	9.0 (7.0-11.3)	9.9 (7.1-13.1)	0.127
Neutrophil count (10^3/μL)	6.7 (4.9-8.5)	7.0 (5.1-9.9)	0.169
Lymphocyte count (10^3/μL)	1.4 (1.0-2.0)	1.4 (0.8-2.3)	0.464
Hemoglobin (g/dL)	11.4 (10.1-12.9)	10.8 (9.4-12.1)	0.016
Hematocrit (%)	36.3 (32.8-40.8)	34.2 (29.8-39.0)	0.012
Mean platelet volume (fL)	87.5 (82.5-91.6)	88.5 (83.5-92.7)	0.277
Blood urea nitrogen (mg/dL)	57.8 (43.9-89.9)	79.2 (53.5-119.8)	<0.001
C-reactive protein (mg/dL)	1.4 (0.5-3.5)	2.3 (0.7-5.9)	0.022
Albumin (g/dL)	3.6 (3.4-3.9)	3.3 (3.1-3.6)	0.002
Creatinine (mg/dL)	1.2 (1.0-1.6)	1.6 (1.1-2.6)	<0.001
Sodium (mEq/L)	138.0 (136.0-141.0)	138.0 (135.0-140.0)	0.112
Potassium (mmol/L)	4.7 (4.3-5.2)	5.0 (4.6-5.5)	0.002
Troponin I (μg/L)	0.0 (0.0-0.1)	0.0 (0.0-0.1)	0.056
Brain natriuretic peptide (pg/mL)	1011.3 (735.8-1779.9)	1484.2 (855.1-2486.3)	0.001
Left ventricular ejection fraction (%)	40.0 (30.0-55.0)	45.0 (35.0-55.0)	0.013
Door to treatment (min)	40.0 (22.0-111.0)	62.5 (30.0-149.2)	0.033
Diuretic use (%)	80 (42.8)	71 (51.4)	0.151
Mortality (%)	16 (8.6)	31 (22.5)	0.001

of independent parameters for predicting hospitalization are presented in Table 4. The ROC curve of parameters and model is shown in Figure 1.

Discussion

We performed this study on 325 HF patients and there was no significant relationship between door to diuretic treatment and short-term mortality. Yet the delay in door to diuretic treatment increased hospitalization rates.

Diuretics is the basis of AHF treatment. Early and rapid treatment in the emergency department is an important step in the management (11). Many studies have confirmed the positive effect of early treatment on the prognosis of patients, and the delay has shown a significant increase in the risk of in-hospital mortality (10). In a retrospective study of more than 700 cases, early IV furosemide treatment was shown to reduce hospital stay (9). A prospective study involving 20 hospitals showed that an increase in door to furosemide treatment time increased the risk of mortality up to the first 100 minutes, and this effect was not seen thereafter. In the same study, early treatment of AHF patients with IV furosemide was independently associated with a reduction in in-hospital mortality (10). On the other hand, by Park et al. (12) concluded that door to diuretic treatment time had no effect on in-hospital, one-month and

Table 3. Door to diuretic treatment cut-off values and odds ratios of mortality and hospitalization

	Cut-off values	Odds ratios	95% confidence intervals	p
Mortality (n=47)	13 min	2.69	1.05-6.89	0.062
Hospitalized (n=138)	99 min	1.75	1.09-2.82	**0.020**

Table 4. Logistic regression analysis of independent parameters for predicting hospitalization.

			95% confidence intervals	
Independent parameters	**p**	**Odds ratio**	**Lower**	**Upper**
Door to treatment time	0.676	1	1	1
Left ventricular ejection fraction	0.022	0.97	0.95	1
C-reactive protein	0.047	0.94	0.88	1
Creatinine	0.003	0.66	0.5	0.87
Brain natriuretic peptide	0.039	1	1	1
Albumin	0.373	1.56	0.59	4.11
Model	**Accuracy**	**Specificity**	**Sensitivity**	**AUC**
	0.74	0.85	0.54	0.800

AUC: Area under the curve

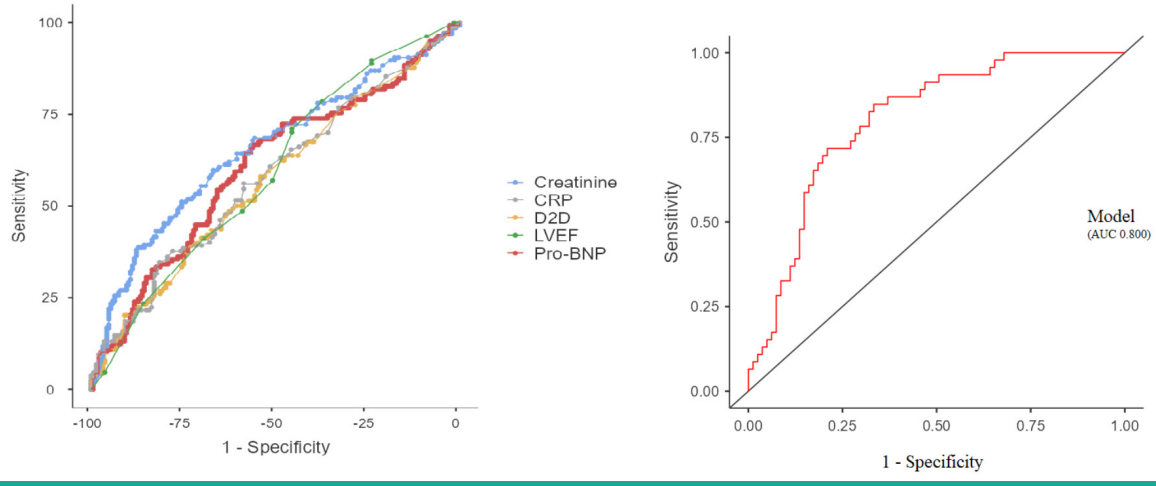

Figure 1. ROC curve of parameters and model

D2d: Door to diuretic treatment, LVEF: Left ventricle ejection fraction, CRP: C-reactive protein, pro-BNP: Pro-B-type natriuretic peptide

one-year mortality. In our study, there was no significant effect on short-term mortality. The biggest reason for this difference may be: AHF has various etiologies and is a syndrome, not a single disease (13). Many reasons, from myocardial infarction to infection, can cause AHF. Diuretic treatment does not give same effect in all HF patients. There are also patients who are diuretic resistant. The inability to fully isolate the patient group who has the same clinical condition and could benefit from diuretic therapy may explain the differences in results in the studies.

HF is one of the leading diseases in hospitalizations worldwide. Since the treatment costs are high, researches have been done to predict hospitalization (14). In our study, we found that the delay in the door to treatment time could predict the need for hospitalization, albeit weakly. There could be many reasons for delay in treatment. One of the reasons is that lung diseases or other cardiac-related diseases that fall into the differential diagnosis of AHF precede the actual diagnosis (15). It can be thought that delayed treatment may cause progression of clinical deterioration and consequently hospitalization.

In our study, left ventricular ejection fraction, C-reactive protein, creatinine, pro-BNP, and albumin were independent predictors. We found that the model formed with these parameters predicted hospitalization more strongly (AUC 0.800). We believe that new models can be developed using these parameters in order to more accurately identify patients who require hospitalization and effectively manage their care.

Study Limitations

There are several important limitations of the study. Most important limitation was that our study had a retrospective design (16). Furthermore, we did not use a classification method, such as the New York Heart Society classification, to group the patients. We did not compare subgroups. Thirdly, we did not evaluate the volume status of the patients. Finally, we could not determine the diuretic resistance of the patients.

Conclusion

According to the results of our study, early diuretic treatment has no effect on short-term mortality. However, the delayed door to treatment may affect hospitalization rates. We recommend early diuretic treatment in AHF patients to use hospital resources efficiently and to reduce hospitalizations. On the other hand, the data of our study should be verified with large multicenter samples.

Ethics

Ethics Committee Approval: Approval for the study was obtained from the Local Ethics Committee of University of Health Sciences Turkey, Ümraniye Training and Research Hospital (no: 426, date: 14/01/2021).

Informed Consent: Since this study was retrospective and the data were randomized, informed consent is not required.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.Ö., K.Ö., A.A., A.C., S.Ö., İ.A., Design: A.Ö., K.Ö., A.A., A.C., S.Ö., İ.A., Data Collection or Processing: A.Ö., K.Ö., A.A., A.C., S.Ö., İ.A., Analysis or Interpretation: A.Ö., K.Ö., A.A., A.C., S.Ö., İ.A., Writing: A.Ö., K.Ö., A.A., A.C., S.Ö., İ.A., Drafting Manuscript: A.Ö., K.Ö., A.A., A.C., S.Ö., İ.A., Final Approval and Accountability: A.Ö., K.Ö., A.A., A.C., S.Ö., İ.A., Technical or Material Support: A.Ö., K.Ö., A.A., A.C., S.Ö., İ.A., Supervision: A.Ö., K.Ö., A.A., A.C., S.Ö., İ.A.

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