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# A Novel Index for Survival in Acute Heart Failure: Diuretic Efficiency Score

## Akut Kalp Yetmezliğinde Sağkalım Değerlendirmek için Yeni Bir Skor: Diüretik Etkinlik Skoru

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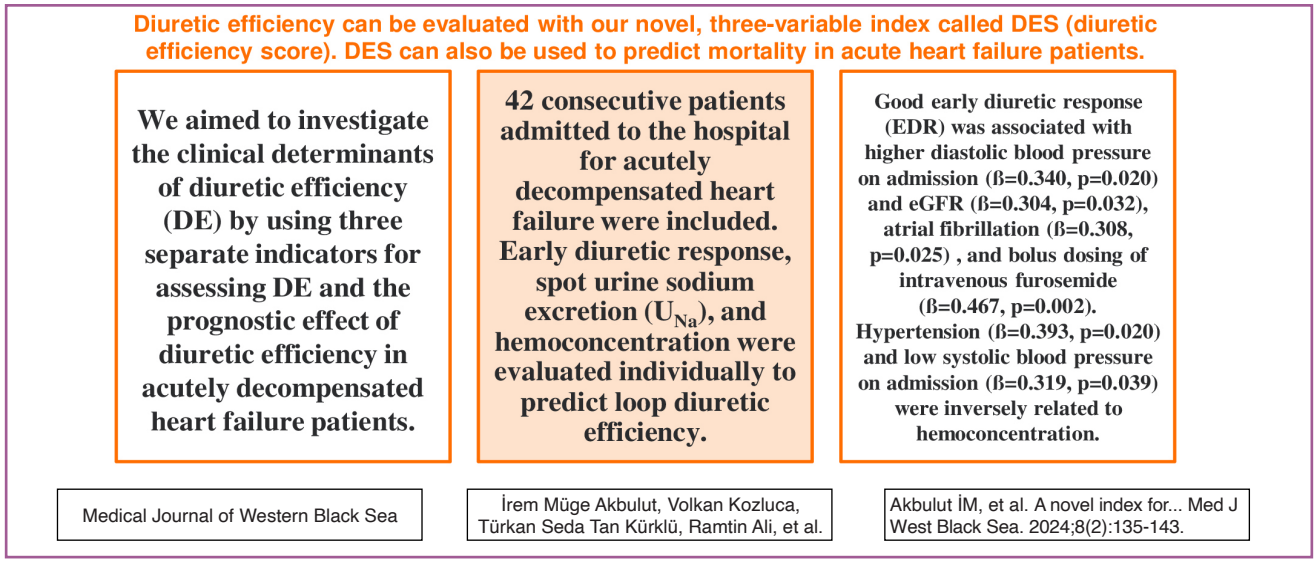
**GRAPHICAL ABSTRACT**




## ABSTRACT

**Aim:** Acute heart failure (AHF) is the leading cause of hospital admissions among adults ≥65. Loop diuretics are the mainstay of treatment of congestion in AHF. Response to loop diuretics is closely related to morbidity and mortality. In this study, we aimed to investigate 1- the clinical determinants of diuretic efficiency (DE) by using three separate indicators for assessing DE and 2-the prognostic effect of diuretic efficiency in acutely decompensated heart failure patients.

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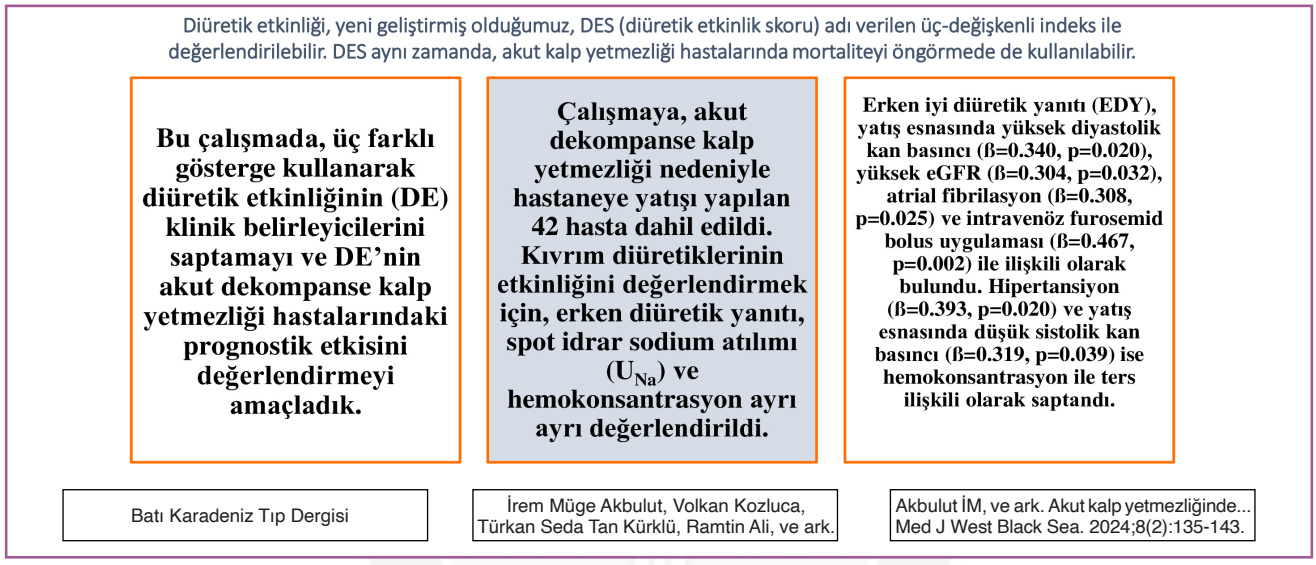
**Material and Methods:** 42 consecutive patients admitted to the hospital for acutely decompensated heart failure were included. Early diuretic response, spot urine sodium excretion (UNa), and hemoconcentration were evaluated individually to predict loop diuretic efficiency.

**Results:** Good early diuretic response (EDR) was associated with higher diastolic blood pressure on admission (ß=0.340, p=0.020) and eGFR (ß=0.304, p=0.032), atrial fibrillation (ß=0.308, p=0.025) , and bolus dosing of intravenous furosemide (ß=0.467, p=0.002). Hypertension (ß=0.393, p=0.020) and low systolic blood pressure on admission (ß=0.319, p=0.039) were inversely related to hemoconcentration.

**Conclusion:** Diuretic efficiency is strongly influenced by the heart rhythm, renal function, blood pressure, prevalence of hypertension, and schedule of furosemide administration. We developed a novel, three-variable index called DES (diuretic efficiency score) that predicts mortality in AHF patients. Future research in larger cohorts is needed to validate DES as a predictor of mortality in heart failure.

**Keywords:** Heart failure, diuretic response, survival

**GRAFİKSEL ÖZET**




## ÖZ

**Amaç:** Akut kalp yetmezliği (AKY) 65 yaş üstü yetişkinlerde hastaneye yatışların en sık nedenidir. Kıvrım diüretikleri, AKY'de konjesyon tedavisinin temel unsurudur. Kıvrım diüretiklerine olan yanıt morbidite ve mortalite ile yakından ilişkilidir. Bu çalışmada;1-üç ayrı gösterge kullanarak diüretik etkinliğinin (DE) klinik belirleyicilerini ve 2-akut dekompanse kalp yetmezliği hastalarında diüretik etkinliğinin prognostik etkisini araştırmayı amaçladık.

**Gereç ve Yöntemler:** Akut dekompanse kalp yetersizliği nedeniyle hastaneye yatırılan 42 hasta çalışmaya dahil edildi. Kıvrım diüretik etkinliğini belirlemek için erken diüretik yanıtı, spot idrar sodyum atılımı (UNa) ve hemokonsantrasyon parametreleri ayrı ayrı değerlendirildi.

**Bulgular:** İyi erken diüretik yanıtı (EDY), başvuru sırasındaki yüksek diyastolik kan basıncı (ß=0.340, p=0.020) ve eGFR (ß=0.304, p=0.032), atriyal fibrilasyon (ß=0.308, p=0.025) ve intravenöz furosemidin bolus doz şeklinde verilmesi (ß=0.467, p=0.002) ile ilişkili olarak tespit edildi. Hipertansiyon (ß=0.393, p=0.020) ve başvuru sırasındaki düşük sistolik kan basıncı (ß=0.319, p=0.039) hemokonsantrasyon ile ters ilişkili olarak bulundu.

**Sonuç:** Diüretik etkinliği kalp ritmi, böbrek fonksiyonu, kan basıncı, hipertansiyon varlığı ve furosemid uygulama şeklinden güçlü bir şekilde etkilenmektedir.Mevcut çalışmada, AKY hastalarında mortaliteyi öngördürmede kullanılabilecek ve DES (diüretik etkinlik skoru) adı verilen yeni, üç değişkenli bir indeks geliştirdik. DES'in kalp yetmezliğinde bir mortalite prediktörü olarak valide edilebilmesi için, ileride daha büyük kohortlarda çalışmaların yapılması gereklidir.

**Anahtar Sözcükler:** Kalp yetmezliği, diüretik yanıt, sağkalım

## INTRODUCTION

Acute heart failure (AHF) is the leading cause of hospitalization among adults ≥65 (1). Both de novo heart failure and acutely decompensated chronic heart failure (ADCHF) may present as AHF. Regardless of the temporal classification, both forms of AHF are associated with substantial 60- to 90-day mortality rates of 7 and 11% and re-hospitalization rates of 25 and 30%, respectively (2).

Congestion (peripheral and/or pulmonary) is the most common presentation and the chief reason for hospital admissions in AHF (3). Parenteral loop diuretics form the mainstay of treatment of congestion in AHF. Response to loop diuretics is generally evaluated by monitoring weight loss, urinary output, and urinary sodium excretion (4). Hemoconcentration has also recently gained popularity as a marker of decongestion, along with other parameters (5). Poor diuretic response or diuretic resistance is defined as reduced sensitivity to loop diuretics, poor natriuresis and diuresis despite escalating doses of diuretics (6). Diabetes mellitus, reduced glomerular filtration rate (GFR), low systolic blood pressure, high blood urea nitrogen levels, more advanced heart failure, and atherosclerotic disease are associated with poor diuretic response (4, 7). Both poor diuretic response and the requirement of higher doses are closely related to residual congestion and increased mortality in heart failure patients (8). Therefore, recognition of poor responders is essential for early treatment modifications and improvement of patient-related outcomes.

In the this study, we aimed to investigate 1-the clinical determinants of diuretic efficiency (DE) by using three separate indicators for assessing DE, 2-the prognostic effect of diuretic efficiency in patients hospitalized for acutely decompensated heart failure.

## MATERIAL and METHODS

In this prospective observational study, a total number of 42 consecutive patients who were admitted to our inpatient cardiology clinic for acutely decompensated heart failure between May 2020 and December 2020 were included. The study overview is represented in Figure 1.

ADHF was diagnosed by the attending physician, as the presence of at least one symptom (peripheral edema, orthopnea, dyspnea, paroxysmal nocturnal dyspnea) and at least one sign (pulmonary crackles, peripheral edema, elevated jugular venous pressure, typical chest radiograph findings of pulmonary edema), based on elevated N-terminal-proBNP levels (>450 g/ml) (6). A history of hospitalization for ADHF within the past 6 months was defined as an unplanned need for parenteral loop diuretic therapy for unresolving heart failure symptoms.

Hypertension was defined as a systolic blood pressure greater than or equal to 140 mmHg and/or a diastolic blood pressure greater than or equal to 90 mmHg. Diabetes mellitus was defined asa fasting blood glucose of greater than or equal to 126 mg/dl, or being on either oral anti-diabetic drugs or insulin treatment.Atrial fibrillation was defined as a sustained irregular supraventricular tachyarrhythmia with the absence of distinct P waves and irregular atrial activations.

The ejection fraction (EF) was defined as the percentage of blood pumped from the left ventricle with each heartbeat and calculated by trans-thoracic echocardiography (TTE).

An ischemic etiology of heart failure was defined as heart failure with reduced ejection fraction due to the presence of obstructive coronary artery disease. A non-ischemic, dilated etiology of heart failure was defined as heart failure with reduced ejection fraction due toetiologies other than atherosclerotic coronary artery disease like toxins, metabolic diseases, alcohol, etc.Heart failure with preserved ejection fraction was defined as signs and symptoms of heart failure owing t high left ventricular filling pressure despite normal left ventricular ejection fraction.

The exclusion criteria were: 1-patients younger than 18 years old, 2- patients on chronic hemodialysis or peritoneal dialysis, 3-patients unable to collect urine properly, 4-patients who received intravenous diuretic therapy in

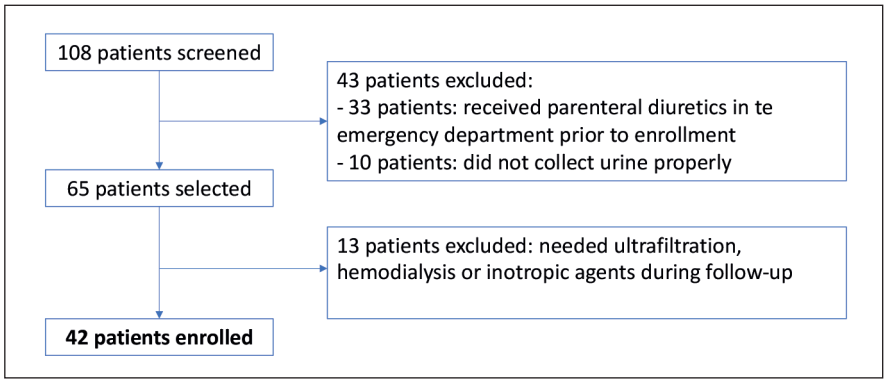



**Figure 1:** The study overview.

the emergency department before enrollment, 5-patients with hemodynamic instability, and 6- patients on inotropic agents.

The study protocol was approved by the local ethics committee (Date: 29/09/2021, Decision No: 2021000333-2) and was performed in concordance with the Declaration of Helsinki. All patients provided written informed consent.

Before the initiation of parenteral loop diuretic therapy, all patients were asked to completely empty their bladders. Next, all patients were started on intravenous furosemide therapy. The dose was determined by the treating physician, according to the volume status and chronic oral diuretic dose of the patient. Following the initiation of the diuretic therapy, a 6-hour urine collection was started. In addition, a spot urine sample was obtained at hour 2 for the determination of urine electrolytes and osmolarity.

Blood samples were collected at baseline, on discharge day, and whenever the treating physician considered it necessary throughout the hospitalization. Weight, urine output, diuretic dose, and hemodynamic data (non-invasive measurement of systolic and diastolic blood pressures and heart rate with an automated oscillometric blood pressure measuring device) were collected daily. A 12-lead surface electrocardiography (ECG) and trans-thoracic echocardiography (TTE) were obtained on the day of admission for each patient. Heart rhythm data was derived from the ECG records, and the left ventricular ejection fraction was calculated from the TTE records. Descriptive variables were noted at baseline.

To assess diuretic efficiency, we used three separate indicators: 1-early diuretic response (EDR), 2-spot urine sodium (Na) excretion ($U_{Na}$), and 3-hemoconcentration.

EDR was defined as net urine output produced per 40 milligrams of intravenous furosemide received (expressed as milliliters of net urine output per 40 mg furosemide equivalent) (9). $U_{Na}$ was obtained at the second hour of the intravenous diuretic therapy from spot urine samples. Hemoconcentration was defined as the change in hematocrit on discharge from admission.

### Statistical Analyses

Statistical analyses were conducted with the Statistical Package for Social Sciences (SPSS) software, version 10.0. To test the normality distribution of the variables the skewness and kurtosis values were calculated. In addition, the data with a significance value of the Shapiro-Wilk Test greater than 0.05 is assumed to have a normal distribution, and parametric tests were applied. For the data with a significance value of less than 0.05, nonparametric tests were done. The results were given as mean ± SEM, whereas categorical ones were given as frequencies and percentages (%). The association between laboratory and clinical parameters was evaluated with Pearson or Spearman correlation analysis concernining the needs of parametric test assumptions. For the association between a continuous variable and a categorical variable, we can used point biserial correlation with Pearson analysis.Linear regression analysis was used to examine continuous outcome data to compare the relative influence of different independent variable on the dependent variable. The standardized coefficients from linear regression analysis were used to rank the predictors of dependent variable.

The overall survival (OS) time was calculated from the start of diuretic treatment till death from any cause. The survival analysis was done by Kaplan-Mayer method. Cox multivariate regression analysis was performed to identify the independent predictors of the overall survival.Variables with a significant or weak association, having a p-value less than 0.2, with overall survival in univariate analysis were incorporated into the multivariate analysis. ROC curve analysis was used to measure the diagnostic accuracy of the determinants used in the study. The Youden index method was used to define the optimal cut-off points for the studied determinants (10).

## RESULTS

### Baseline Characteristics

The baseline characteristics of patients are presented in Table 1. The measurable clinical and lab parameters were normally distributed with similar mean and median values except N-terminal-prohormone BNP levels, which originated from the wide range of levels of plasma BNP fluctuation over the determined pathological cut-off levels. The skewness (J value; Karl Pearson's Coefficient of skewness) and kurtosis (ß2 value) values of the variables, excluding BNP, were between 0.2 and 1.7. Therefore, we included the median values of the parameters for the homogeneity of Table 2.

The median length of stay in the hospital was 6 days (range: 1 - 24 days). The median parenteral furosemide dose was 120 mg (range: 40 - 960 mg). 35.7% of the patients received only bolus doses of furosemide. 38.1% of the patients received continuous infusion, whereas 26.2% of the patients received a combination of infusion and boluses. The median urine osmolarity at hour 2, was 282 mOsm/kg (range: 155-709 mOsm/kg), and the median urine output after 6 hours was 1100 mL (range: 100 to 4000 mL). The performance of the determinants of diuretic response was evaluated by ROC analysis. The hemoconcentration, early diuretic response, and spot urinary Na excretion were the most prominent determinants of diuretic efficiency (AUC's 0.745±0.084&0.718±0.068&0.660±0.086 respectively, p values

0.012&0.021&0.081 respectively, cut-off values -0.20&350 ml&72 mEq/L respectively) (Figure 2). The cutoff levels of the prominent determinants of diuretic efficiency were chosen as the values providing the best tradeoff between sensitivity and specificity, providing the maximum Youden index (sensitivity+specificity-1) from the ROC tables (Figure 2).

**Table 1:** The baseline characteristics of the patients.

| Characteristic | Findings (n=42) |
|---|---|
| Age, years (mean±SEM) | 68.5 (2.3) |
| Female | 18 (42.9) |
| History of hospitalization for ADHF in the past 6 months | 12 (28.6) |
| **Co-morbidities** | |
| Hypertension | 30 (71.4) |
| Diabetes mellitus | 20 (47.6) |
| Atrial fibrillation | 18 (42.9) |
| **EF** | |
| <40% | 28 (65.9) |
| ≥40% | 14 (34.1) |
| **Etiology of heart failure** | |
| Ischemic | 18 (42.9) |
| Non-ischemic, dilated | 14 (33.3) |
| HFpEF | 10 (23.8) |
| **Home medications** | |
| Furosemide only | 28 (66.7) |
| Torasemide* only | 5 (11.9) |
| Furosemide+torasemide | 2 (4.8) |
| None | 7 (16.7) |
| **Clinical presentation on admission** | |
| Heart rate (Beat/min±SEM*)* | 87.2±3.2 |
| Weight, kg±SEM | 82.7±2.2 |
| Oxygensaturation, %±SEM | 90.0±1.2 |
| Systolic blood pressure, mmHg±SEM | 120.0±3.6 |
| Diastolic blood pressure, mmHg±SEM | 74.5±2.9 |
| Pulse pressure, mmHg±SEM | 43.4±1.9 |
| **Laboratory parameters on admission** | |
| Serum sodium (Na), mEq/L±*SEM* | 135.1±1.1) |
| Serum chloride (Cl), mEq/L±SEM | 99.8±1.1) |
| eGFR (CKD-EPI), ml/min per 1.73 $m^2$±SEM | 59.3±4.0) |
| NT-proBNP, pg/ml±SEM | 8819.0±1549.0 |
| Serum hematocrit, %±SEM | 37.1±1.0 |
| Serum albumin, gr/L±SEM | 36.2±0.6 |
| ***Loop diuretic dose, mg** | 124.6±35.2 |

**EF:** Ejection fraction, **HFpEF:** Heart failure with preserved ejection fraction, **eGFR:** Estimated glomerular filtration rate, **NT-proBNP:** N-terminal-prohormone BNP, **SEM:** Standard Error of Mean.

*The dose of oral torasemide was presented as oral furosemide-equivalent (assuming 20 mg of oral furosemide was equivalent to 40 mg of oral furosemide).

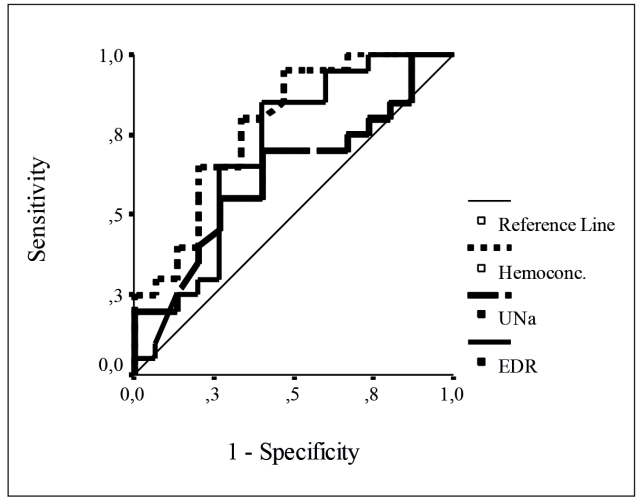



**Figure 2:** The ROC curves of the determinants of the diuretic effiency.

### Renal Function and Loop Diuretic Dosing Scheme Affect Diuretic Response

We assessed three indicators for diuretic efficiency: early diuretic response (EDR), natriuresis ($U_{Na}$) and hemoconcentration. We tested both clinical and laboratory parameters as the predictors of those indicators.

Heart rhythm, ejection fraction, diastolic blood pressure on admission, serum sodium and chloride levels on admission, eGFR, and loop diuretic scheme were included as the predictor parameters of early diuretic response. The results of the univariable and multivariable regression model of predictors of early diuretic response are shown on Table 2.

The early diuretic response was better in patients with AF, higher diastolic blood pressure, and better renal function on admission. In addition, bolus dosing of furosemide, rather than a continuous infusion or combination therapy, was associated with better early diuretic response. Although the patient characteristics including co-morbidities, etiology of heart failure, home medications were also tested as predictors, none of them was found significant in predicting EDR. Likewise, serum sodium, chloride and NT-proBNP levels were not associated with EDR.

The clinical parameters did not affect natriuresis in heart failure patients. Though serum sodium and chloride levels on admission were positively related to natriuresis on univariate analysis, none of the variables were found to be independently significant on natriuresis (Table 2).

Although diabetes mellitus and poor renal function were associated with lower hemoconcentration on univariate analysis, these parameters did not affect hemoconcentration independently on multivariate analysis. On the other hand, blood pressure was the only independent predictor

**Table 2:** Predictors of early diuretic response, natriuresis, and hemoconcentration in univariate ant multivariate analyses.

| Variables | Correlation coefficient | p | Standardized coefficients | p |
|---|---|---|---|---|
| Heart rhythm | 0.2888 | 0.084 | 0.308 | 0.025* |
| Ejection fraction (EF) | 0.262 | 0.123 | 0.251 | 0.071 |
| Diastolic blood pressure on admission | 0.306 | 0.066 | 0.340 | 0.020* |
| Serum Na on admission | -0.223 | 0.105 | 0.246 | 0.291 |
| eGFR | 0.241 | 0.150 | 0.304 | 0.032* |
| Serum Cl on admission | 0.227 | 0.196 | 0.332 | 0.133 |
| Loop diuretic scheme | -0.431 | 0.008* | 0.467 | 0.002* |
| **Predictors of natriuresis** | | | | |
| Diastolic blood pressure on admission | 0.229 | 0.156 | 0.171 | 0.220 |
| Serum Na on admission | 0.524 | 0.001* | 0.164 | 0.459 |
| eGFR | 0.103 | 0.234 | 0.125 | 0.365 |
| Serum Cl on admission | 0.521 | 0.001* | 0.303 | 0.078 |
| Loop diuretic scheme | -0.160 | 0.325 | 0.223 | 0.113 |
| **Predictors of hemoconcentration** | | | | |
| HT | -0.437 | 0.006* | 0.393 | 0.020* |
| DM | -0.378 | 0.019* | 0.207 | 0.210 |
| Etiology of heart failure | 0.294 | 0.074 | 0.030 | 0.852 |
| Systolic blood pressure on admission | 0.250 | 0.130 | 0.319 | 0.039* |
| eGFR | 0.277 | 0.007* | 0.034 | 0.838 |

**EF:** Ejection fraction, **eGFR:** Estimated glomerular filtration rate, **HT:** Hypertension, **DM:** Diabetes mellitus.
*p<0.05

of hemoconcentration (Table 2). Both high and low blood pressure values on admission were inversely correlated with hemoconcentration.

### Diuretic Efficiency Score (DES) Predicts the Survival of Patients with Heart Failure

Median follow-up time for the patients was 12 months. The 6-month mortality rate was 37.5% (15 patients). Early diuretic response, spot urinary sodium excretion at hour 2, and hemoconcentration were used as the indicators of diuretic efficiency. None of those parameters significantly predicted the overall survival of the patients (respectively, p=0.325, p=0.243, p=0.057).

EDR, UNa, and hemoconcentration were scored as 0 for patients with values lower than the cut-off values, providing the best tradeoff between sensitivity and specificity and the maximum Youden index from ROC analysis (Figure 2). Patients with values equal to or higher than the cut-off values were scored as 1. We've developed a diuretic efficiency score (DES) regarding the sum of the scores of those three parameters. Patients having 0-1 points were referred as low DES and 2-3 as high DES. Patients with high DES had significantly longer overall survival time than the low DES group (Figure 3). The DES was the only independent predictor of overall survival on Cox regression analysis (p=0.07).

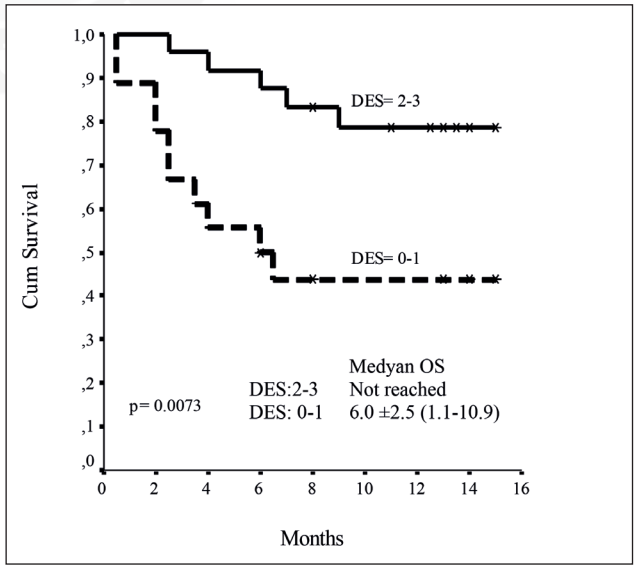



**Figure 3:** The survival curves according to the Diuretic Efficiency Score (DES) levels.

## DISCUSSION

Parenteral loop diuretics remain the cornerstone of treatment of congestion in AHF. Effective decongestion is mandatory to achieving symptom control and reducing recurrent hospitalizations in AHF patients. However, it remains difficult to accurately assess the treatment efficacy due to the paucity of specific criteria for evaluating congestion. Recently, several parameters like weight loss, net fluid loss, urine output, urinary sodium excretion, change in natriuretic peptide concentration, and hemoconcentration have been proposed as surrogate markers of decongestion in heart failure patients receiving diuretics (6,11,12).

Poor diuretic response (diuretic resistance, DR) remains a frequent obstacle to obtaining effective decongestion and portends a poorer prognosis in AHF. Impaired renal function, diabetes mellitus, atherosclerotic disease, low systolic blood pressure were previously shown as common risk factors for DR (13,14). Therefore, establishing risk factors for DR is vital to predicting patients in need of higher diuretic doses and early treatment modifications.

The present study showed that higher diastolic blood pressure and atrial fibrillation on admission, better renal function, and pulse dosing of furosemide instead of continuous infusion were associated with good early diuretic response. Our study also revealed that hemoconcentration, another good indicator of decongestion, was notably worse in patients with hypertension and patients with lower systolic blood pressure on admission. In addition, although serum sodium and chloride levels were positively related to urinary sodium excretion on univariate analysis, after multivariable adjustments, none of the variables were significantly related to natriuresis in multivariate analysis. We developed a novel, 3-variable index called DES (diuretic efficiency score) that is composed of the parameters: EDR, $U_{Na}$ and hemoconcentration. DES performs quite well in predicting survival inacutely decompensated HF patients.

### Determinants of Early Diuretic Response

In this study, lower eGFR and diastolic blood pressure values on admission were associated with a more unsatisfactory diuretic response, in line with previous studies (8, 12-15). Surprisingly, patients with AF had better early diuretic response compared to the patients in sinus rhythm, after adjustment for other covariates. To our knowledge, no prior studies have examined the role of heart rhythm on diuretic response. We speculate that this finding might be due to elevated atrial natriuretic peptide (ANP) levels observed in patients with AF (15-17). Elevated ANP levels may have triggered diuresis in patients with AF in our study.

The most efficacious schedule of administration of intravenous loop diuretics is still controversial. In the DOSE trial, there was no significant difference between continuous infusion and bolus dosing in terms of efficacy (18). On the other hand, in a recent meta-analysis including 735 patients, the continuous infusion of loop diuretics was associated with better net urine output and weight loss (19). Surprisingly in our study, the early diuretic response was better in patients receiving bolus dosing compared to continuous infusion or the combination of both. One possible explanation for this finding may be the use of continuous infusion in patients with more advanced heart failure who have greater diuretic resistance, by the treating physician. It should also be noted that the bolus group tended to receive a lower total dose of diuretics than the other groups.

### Determinants of Urinary Sodium Excretion

In a recent position paper from the European Society of Cardiology, determining of spot urine sodium content after 2 hours is recommended to interpret the diuretic response in AHF patients. Generally, a spot urine sodium concentration lower than 50-70 mEq/L after 2 hours indicates a patient with a poor diuretic response and needs treatment intensifications (6). Similarly, in a prospective registry including 669 patients, patients with lower urinary Na excretion had less net fluid and weight loss. During follow-up, these patients were also at higher risk for all-cause death and worsening heart failure (20). Therefore, early urinary sodium excretion stands as an essential indicator of diuretic response. The serum sodium and chloride levels on admission were positively related to natriuresis. However, nor the serum Na and chloride levels neither the clinical and hemodynamic variables were found to be independent predictors of natriuresis on multivariate analysis.

### Determinants of Hemoconcentratiom

Hemoconcentration is a surrogate marker of effective decongestion and diuresis in patients hospitalized for heart failure. A series of studies have indicated that hemoconcentration during hospitalization is closely related to less re-admission and mortality rates (21-23). In addition, the prevalence of hypertension and low systolic blood pressure on admission was inversely correlated with hemoconcentration in our patients both on univariate and multivariate analyses. We also found a negative relationship between the prevalence of DM and poor renal function and hemoconcentration on univariate analysis, but not in multivariate analysis. In line with previous studies, our results also demonstrated a nonsignificant relationship between hemoconcentration and survival.

### Diuretic Efficiency Score (DES) Predicts Survival

Acute heart failure is the primary cause of mortality in hospitals. Clinical, hemodynamic, and laboratory parameters have been used to develop clinically useful risk stratification. The risk stratification of patients with AHF may improve the

**Table 3:** Cox regression analysis for the parameters.

| Parameter | Adjusted Odds Ratio (95% CI) | p |
|---|---|---|
| DM | 1.742 (0.538 – 5.645) | 0.355 |
| Rhythm | 0.851 (0.299 – 2.416) | 0.761 |
| Ejection Fraction | 1.312 (0.411 – 4.193) | 0.647 |
| Diastolic Blood Pressure on admission | 1.001 (0.948 – 1.058) | 0.958 |
| eGFR | 0.978 (0.953 – 1.004) | 0.097 |
| Serum $Na^+$ level on admission | 0.937 (0.869 – 1.010) | 0.088 |
| DES | 0.262 (0.078 – 0.881) | 0.030 |

**CI:** Confidence interval, **DM:** Diabetes mellitus, **eGFR:** Estimated glomerular filtration rate, **Na:** Sodium, **DES:** Diuretic efficiency score.

outcome and avoid inappropriate early discharge of high-risk patients. The variables, including age, blood pressure, sodium concentration, hemoconcentration, and renal function, have been included in many clinical scoring systems evaluating patients' risk with AHF. In the current study, we could not find a significant correlation between the clinical, hemodynamic, and laboratory parameters (Table 1) and the survival of the patients. The early response to treatment is a significant predictor of outcomes in patients with AHF. We evaluated the parameters of response, such as diuretic response, urinary Na excretion, and hemoconcentration, as predictors of survival. However, none was found to be significant on univariate analysis, but the diuretic efficiency score developed in the current study (Table 3).

In order to better predict the overall survival of HF patients in relation to their diuretic response, we developed a novel index called "diuretic efficiency score (DES)" by combining the parameters: early diuretic response, urinary Na excretion and hemoconcentration. Patients with low DES (0-1) had significantly lower overall survival time than patients with high DES (2-3) (Figure 3). Likewise, the DES was the only independent predictor of overall survival on Cox regression analysis (Table 4). To the best of our knowledge, our study is the first in combining the three different indicators for the evaluation of diuretic responsiveness in HF and establishing a scoring system for prediction of survival in relation to diuretic efficiency.

The present study has some limitations. First, it was a single-center study with a small cohort. Secondly, the follow-up time was relatively short of predicting the long-term outcomes accurately. Lack of a stratified analysis of groups according to ejection fraction due to the small sample size is another limitation of our study.

In conclusion, an early diuretic response is strongly influenced by the heart rhythm, renal function, diastolic blood pressure, and schedule of furosemide administration. Also, hemoconcentration, a relatively novel surrogate of decongestion, is negatively affected by the prevalence of hypertension and low systolic blood pressure on admission.

Despite the limitations, our study is valuable for 1-evaluating diuretic efficiency with three separate surrogate markers of decongestion, 2-investigating the hemodynamic and clinical factors affecting each parameter individually, and 3-developing a novel index (DES) that accurately predicts survival in HF patients. However, the DES that we defined in the current study needs to be further evaluated with larger cohorts.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None.


## Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

## Conflicts of Interest

The authors have no conflicts of interest to declare.


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## Ethical Approval

The study was initiated with the approval of the Ankara University Medical Faculty Clinical Researches Ethics Committee (Date: 29/09/2021, Decision No: 2021000333-2).Written informed consent forms were obtained from all of the patients.

## Review Process

Externally and extremely peer-reviewed.

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