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The role of biochemical markers in predicting worsening heart failure; comparison of biomarkers

Kötüleşen kalp yetmezliğini öngörmede biyokimyasal belirteçlerin rolü; biyobelirteçlerin karşılaştırılması

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Abstract: Objective: Heart failure is the end stage of many cardiac disorders. Worsening heart failure causes high mortality in these patients. In the present study, we aimed to elucidate and compare the biochemical predictors of worsening heart failure.

Methods: One hundred one patients with heart failure were included in this study. Patients were divided into two groups according to their functional status. N-terminal pro-brain natriuretic peptide (NT-pro BNP), troponin T, serum and urine creatinine, blood urine nitrogen (BUN), eGFR, cystatin C, neutrophil gelatinase associated lipocalin (NGAL), C-reactive protein, hepatic transaminases and thyroid stimulating hormone levels were measured.

Results: NT-pro BNP, troponin T, serum creatinine, BUN, cystatin C and NGAL levels were significantly higher but urine creatinine level and eGFR was lower in decompensated heart failure patients. In univariate analysis, age, cystatin C, NGAL, NT-pro BNP and serum creatinine and eGFR predicted worsening heart failure (WHF). In multivariate analysis, cystatin C and NT-pro BNP variables were found to be significant in predicting WHF. However, eGFR were determined at the limit of significance (p=0.053) with an high odds ratio 3.173 (95% CI:0.983–10.240). Cystatin C and NT-pro BNP concentrations were predictors of worsening heart failure. In ROC analysis, cystatin C is a better predictor of decompensated heart failure compared with NT-pro BNP and other predictors, and has a sensitivity of 82% and a specificity of 63%.

Conclusion: This study revealed that cystatin C and NT-pro BNP were significant predictors of WHF, and cystatin C is slightly better predictor of WHF. Further studies are needed to confirm these results.

Keywords: Heart failure, cystatin C, NT-pro BNP, NGAL, creatinine, eGFR

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Özet: Amaç: Kalp yetmezliği birçok kalp hastalığının son aşamasıdır. Kötüleşen kalp yetmezliği bu hastalarda yüksek mortaliteye neden olmaktadır. Biz bu çalışmada kötüleşen kalp yetmezliğinin biyokimyasal belirleyicilerini ortaya koymayı ve karşılaştırmayı amaçladık.
**Materials and Methods**

This single center crossover observational study was conducted at a tertiary heart center. A total of 101 patients with systolic heart failure (left ventricular ejection fraction <50%) who had proper inclusion criteria were recruited to the study. Patients were randomly selected and divided into two groups according to their functional status. According to New York Heart Association Functional Classification, class 1 and 2 patients were included in group 1 as compensated heart failure, and class 3 and 4 patients were included in group 2 as decompensated heart failure. Compensated heart failure group consisted of 57 (56.7%) patients, and decompensated heart failure group included 44 (43.6%) patients. After inclusion, demographic properties and clinical histories of the patients were inquired. Blood and urine samples were also obtained for biochemical analyzes. Exclusion criteria of the present study were cardiogenic shock, complete AV block on admission, acute coronary syndrome, need for emergent coronary artery bypass surgery, severe bronchospastic airway disease, known renal failure (creatinine >1.5 mg/dl or >132.6 μmol/L), hepatic dysfunction, chronic inflammatory diseases, malignancies, active infections, endocrine or metabolic disorders except diabetes mellitus. Patients taking corticosteroids, statins in the last 3 months, anti-oxidant vitamins and alcohol were also excluded from the study. The study protocol was approved by the local ethics committee and written informed consent was taken from all patients. The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) guidelines.

**Blood sampling**

Overnight fasting venous blood samples of all subjects were collected from 08:00 to 12:00 a.m. in plain and ethylene diamine tetra-acetic acid (EDTA) added tubes. All plain tubes were centrifuged at 1400 rcf for 10 minutes within 30 min of collection. N-terminal pro-brain natriuretic peptide (NT-pro BNP), high sensitive troponin T, creatinine, blood urea nitrogen (BUN), cystatin C, C - reac-

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**Introduction**

Heart failure (HF) is the end stage of many cardiac disorders and influences 1 to 2 percent of general population, and the prevalence of HF increases with advanced age to 8 to 10 percent over 75 years of age [1]. The annual mortality rate of HF ranges from 5% to 75% in end-stage cases [2,3]. Approximately, 30% of the patients with acute decompensated heart failure have mild to moderate kidney dysfunction [4]. Decompensated worsening heart failure (WHF) causes high mortality in these patients [2,3]. Cardiac biomarkers play an important role in heart failure. The family of natriuretic peptides, especially B-type natriuretic peptide and its precursor N-terminal pro-brain natriuretic peptide (NT-pro BNP), cystatin C, eGFR (glomerular filtration rate), cardiac troponins and neutrophil gelatinase associated lipocalin (NGAL) were identified as a valued diagnostic and prognostic tool for heart failure [4–7]. However, neither of which has been shown as a criterion of worsening heart failure. In the present study, we aimed to elucidate the biochemical predictors of WHF.

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**Methods and Materials**

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**Blood sampling**

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C-reactive protein (CRP), hepatic transaminases and thyroid stimulating hormone concentrations were measured from serum samples, whereas neutrophil gelatinase associated lipocalin (NGAL) measurement was performed from whole blood samples with EDTA. Serum creatinine, BUN, aspartate transaminase (AST), alanine transaminase (ALT), cystatin C were analyzed with Cobas-C 501 biochemical analyzer (Roche Diagnostics, USA) using original Roche kits, whereas cystatin C levels were measured by immunoturbidimetric method [8]. CRP analysis was performed using BN Prospect nephelometry (Siemens, Germany) and NGAL measurement was performed by Triage device (Biosite Inc., USA) with immunofluorescence method using fluorescent antibody conjugates in a second venous blood sample using K3 EDTA tube [9]. NT-pro BNP test was performed using an electro-chemiluminescence sandwich immunoassay (ECLIA, Roche Diagnostics) on a Modular analytics Hitachi Cobas 6000 [10]. High sensitive troponin T levels were measured by Cobas e 411 analyzer (Roche Diagnostics, USA) with chemiluminescence method [11]. Glomerular filtration rate (eGFR) is used in this study instead of creatinine, because creatinine is affected from age, gender and muscle mass. eGFR was calculated via the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and reported as ml/min.

Values are reported as means±SD, median (interquartile range) or number or percentage of patients, *Student’s t-test, Mann-Whitney U test, Chi-square tests.

| Variables                        | Compensated HF (n=57) | Decompensated HF (n=44) | *p  |
|----------------------------------|-----------------------|-------------------------|-----|
| Age, years                       | 65.9±11.6             | 70.7±10.1               | 0.033|
| Body mass index, (kg/m²)         | 27 (7)                | 26 (5)                  | 0.109|
| Gender, female, n (%)            | 34 (59.6)             | 29 (65.9)               | 0.520|
| Hypertension, n (%)              | 25 (43.9)             | 20 (45.5)               | 0.873|
| Diabetes mellitus, n (%)         | 11 (19.3)             | 9 (20.5)                | 0.885|
| Coronary artery disease, n (%)   | 34 (59.6)             | 27 (61.4)               | 0.861|
| Atrial fibrillation, n (%)       | 31 (54.4)             | 21 (47.7)               | 0.507|
| Ejection fraction, %             | 34.2±5.1              | 33.3±5.0                | 0.410|

Values are presented as mean±SD, median (interquartile range) or number or percentage of patients, *Student’s t-test, Mann-Whitney U test, Chi-square tests.

Statistical analyses were performed using the SPSS software version 17.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk’s test) to determine the normal distribution. Descriptive analyses are presented using means and standard deviations or median and the interquartile range (IQR, range from the 25th to the 75th percentile). The categorical variables are expressed as numbers and percentages. Numerical variables were compared using the Student’s t-test or Mann–Whitney U test. Categorical data were compared with the chi-square test.

A multiple logistic regression analysis that included variables with p<0.1 was performed to identify independent predictors of decompensated heart failure. The capacity of serum cystatin C, NGAL, NT pro-BNP, troponin T, creatinine and eGFR values in predicting presence of decompensated heart failure were analyzed using Receiver Operating Characteristics (ROC) curve analysis where Bonferroni corrected results were used. P value of less than 0.05 was considered significant.

## Results

The demographic and clinical characteristics of the two groups were shown in Table 1. There were no statistically significant differences between two groups except age. The laboratory findings of the patients were shown in Table 2. NT-pro BNP, troponin T, cystatin C, NGAL, BUN and serum creatinine concentrations were significantly higher but eGFR was lower in decompensated heart failure patients.

In univariate analysis, age, cystatin-C, NGAL, NT-pro BNP, troponin T, serum creatinine and eGFR predicted WHF (Table 3). When these factors found significant in predicting WHF in univariate analysis were included in multivariate analysis, it was seemed that the model is significant and the explanatory coefficient of the model were at a good level (63.7%). In this model, cystatin C and NT-pro BNP variables were found to be significant in predicting WHF in multivariate analysis. However, eGFR were determined at...
the limit of significance (p=0.053) with an high odds ratio 3.173 (95% CI:0.983–10.240). Age, NGAL and troponin T were not found to be significant predictors of WHF in multivariate analysis. Cystatin C and NT-pro BNP were independent predictors of WHF. Cystatin C, NT-Pro BNP and e-GFR were included in a logistic regression model. Prediction accuracy of cases according to the model acquired from logistic regression was reported in Table 4.

According to ROC curve analysis: In patients with cystatin C concentrations ≥1.30 mg/L, cystatin C had 81.82% sensitivity, 63.16% specificity, 63.16% positive predictive value (PPV), 81.82% negative predictive value (NPV) and 0.800 Area Under the Curve (AUC) value in predicting WHF. In patients with NT pro BNP concentrations ≥2020 ng/L (≥238.36 pmol/L), NT pro BNP had 68.18% sensitivity, 78.57% specificity, 71.43% PPV, 75.86% NPV and 0.744 AUC value in predicting WHF. It was also found that cystatin C is better predictor of WHF compared with NT-pro BNP and other predictors if the cut off value of cystatin C is accepted as ≥1.30 mg/L. The results of ROC analysis and the cut off values of predictors in predicting WHF were presented in Table 5 and Figure 1.

Statistically significance was observed between AUC values according to cystatin C levels and creatinine

| Table 2: Laboratory findings of patient groups. |
|-----------------------------------------------|
| Variables | Compensated HF (n=57) | Decompensated HF (n=44) | \*p |
| NT-pro BNP (pg/mL) | 1091 (1227) | 4445 (6970) | <0.001 |
| NT-pro BNP (pmol/L) | 128.738 (144.786) | 524.51 (822.46) |
| Troponin T (ng/mL) | 0.013 (0.017) | 0.029 (0.037) | 0.002 |
| Serum creatinine (mg/dL) | 0.9 (0.30) | 1.0 (0.50) | 0.006 |
| Serum creatinine (μmol/L) | 79.56 (26.52) | 88.4 (44.2) |
| BUN (mg/dL) | 18 (9) | 23 (23) | 0.003 |
| BUN (mmol/L) | 6426 (3213) | 8211 (8211) |
| AST (U/L) | 23 (9) | 23 (12) | 0.816 |
| ALT (U/L) | 17 (14) | 17 (11) | 0.469 |
| CRP (mg/L) | 6 (9) | 9 (19) | 0.134 |
| CRP (μmol/L) | 6000 (9000) | 9000 (19000) |
| TSH (mIU/L) | 1.5 (1.5) | 1.4 (1.3) | 0.862 |
| Urine creatinine (mg/dL) | 110 (99) | 87 (82) | 0.015 |
| Urine creatinine (μmol/L) | 9724 (8751.6) | 7690.8 (7248.8) | <0.001 |
| Cystatin C (mg/L) | 1.26 (0.24) | 1.66 (0.78) |
| NGAL (ng/mL) | 67 (28) | 114 (124) | <0.001 |
| eGFR (ml/min) | 71 (26) | 55.1 (40.3) | <0.001 |

Data are presented as median (interquartile range), \*Mann-Whitney U test.

| Table 3: Determination of heart failure predictors by univariate and multivariate analysis. |
|-----------------------------------------------|
| Variables | Univariate analysis | Multivariate analysis |
| | OR | CI 95% | p | OR | CI 95% | p |
| Age | 1.042 | 1.003–1.083 | 0.036 |
| Gender | 0.265 | 0.388–1.732 | 0.520 |
| Diabetes | 1.075 | 0.402–2.878 | 0.885 |
| Hypertension | 1.067 | 0.486–2.353 | 0.873 |
| Coronary artery disease | 1.074 | 0.480–2.403 | 0.861 |
| Atrial fibrillation | 1.306 | 0.594–2.873 | 0.507 |
| Cystatin C (≥130) | 7.714 | 3.025–19.674 | 0.001 |
| NGAL (≥88) | 4.070 | 1.764–9.407 | 0.002 |
| NT-pro BNP (≥2020) | 7.857 | 3.195–19.324 | 0.001 |
| Troponin T (≥0.021) | 4.954 | 2.118–11.590 | 0.001 |
| Creatinine (≥1.30) | 12.833 | 2.732–60.279 | 0.001 |
| GFR (<55) | 8.500 | 3.029–23.854 | 0.001 |

\*Logistic regression analysis (backward elimination method was used).
p = 0.042. No difference was found between the rest of the AUC levels. (p > 0.05) Table 6 and Figure 1. The coefficients of variation values were presented in Table 7. Medications of patients are listed in Table 8.

**Discussion**

The present study revealed that cystatin-C, NGAL, NT-pro BNP, serum creatinine concentrations, eGFR and age predicted WHF in univariate analysis, but cystatin C and NT-pro BNP concentrations were predictors of WHF in multivariate analysis. The study also showed that cystatin C is better predictor of decompensated heart failure compared with NT-pro BNP and other predictors in predicting WHF.

The strength of this study comes from the comparison of biomarkers in predicting worsening of heart failure. An increase in serum creatinine seems in 20 to 40% of patients hospitalized for HF, and is related to chronic kidney disease, history of HF, diabetes mellitus, significant anemia, male gender, elderly age, hypertension and hypotension [12,13]. High concentrations and large increases in serum creatinine point out a longer hospital stay, higher decompensation, re-hospitalization and mortality rates [13]. However, some studies did not show an independent association between an increase in serum creatinine and outcomes [14–16]. Increases in serum cre-
psychosomatic dysfunction associated with the use of angiotensin converting enzyme inhibitors, angiotensin receptor blockers and high dose diuretic therapy have not been found adverse outcomes [14–16]. Our results are consistent with these reports. NGAL is produced by the kidney after ischemic or toxic injury and has been identified as an early marker of acute kidney injury [13]. It has been reported that elevated NGAL concentrations can predict the development of worsened renal function and may be a prognostic marker in patients with HF [17–19].

Cystatin-C is a serum protein produced steadily by all types of nucleated cells and is filtered from the blood by the kidneys and serves as a measure of kidney function. Its low molecular mass allows it to be freely filtered by the glomerular membrane in the kidney, and then it is reabsorbed by the tubular epithelial cells and is catabolized in these cells. It is an index of the GFR and is a more sensitive marker of renal function than creatinine. It has a greater sensitivity for the early detection of kidney dysfunction [13]. It has been shown that cystatin C is a strong predictor of systolic heart failure [20,21] and is associated with the severity of heart failure and coronary artery disease [22,23]. Our results are similar in previous studies of cystatin C. Brain natriuretic peptide (BNP) and its precursor NT-pro BNP have received increasing interest as cardiac markers, both are produced by enzymatic cleavage of the precursor hormone pro-brain natriuretic peptide (pro BNP). Pro BNP is mainly released from ventricular myocytes upon activation of the BNP gene which is induced by excessive stretching of the ventricles due to volume overload and increased filling pressure [24]. It has been well demonstrated that NT-pro BNP is a strong and independent prognostic marker across the spectrum of HF stages and serial NT-pro BNP concentrations provide incremental risk stratification [25]. Our results support previous studies on NT-pro BNP in patients with HF. In the logistic regression model including eGFR, NT-pro BNP and cystatin C, sensitivity was lower but specificity was higher compared with cystatin C in predicting decompensated heart failure and the diagnostic accuracy of the model was 73% in this study (Table 4).

The present study has several limitations. This was a single center study. The sample size in our study was relatively small. Long term follow up data were not evaluated to reveal the clinical and prognostic importance of the results. Despite all the limitations, our study comparing the power of biomarkers in predicting decompensated heart failure provides important contribution to early prediction of WHF.

In conclusion; the study revealed that cystatin C and NT-pro BNP are significant predictors of decompensated heart failure, and cystatin C is slightly better predictor of WHF and has 82% sensitivity and 63% specificity in predicting of WHF. Further studies are needed to confirm these results.

Conflict of Interest: The authors have no conflict of interest.
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