# The relationship between adiponectin, NT-pro-BNP and left ventricular ejection fraction in non-cachectic patients with systolic heart failure: an observational study

## *Kaşektik olmayan sistolik kalp yetmezlikli olgularda adiponektin, NT-pro-BNP ve sol ventrikül ejeksiyon fraksiyonu arasındaki ilişki: Gözlemsel bir çalışma*

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## ABSTRACT

**Objective:** NT-pro-brain natriuretic peptide (NT-proBNP) has been shown to be an accurate diagnostic marker in patients with heart failure (HF). Adiponectin (Adp) levels are increased in HF but its diagnostic value is still uncertain in these patients. The study was designed to investigate the possible association of these markers in non-cachectic patients with newly diagnosed systolic heart failure.

**Methods:** Fifty-seven systolic HF patients and 20 matched controls were enrolled in an observational cross-sectional study. Physical and echocardiographic examinations were performed and serum Adp, NT-proBNP, tumor necrosis factor-alpha (TNF-α) levels were measured. Study variables were compared between the groups. Correlation analyses were done and the diagnostic validity of the markers was compared with ROC analysis.

**Results:** Adp and NT-proBNP levels were significantly higher in HF group (20.19±12.9 vs. 7.65±4.6 µg/mL; p<0.001 and 1051.74±606.2 vs. 222.53±65.6 pg/mL; p=0.002; respectively). TNF-α levels were similar between the groups (2.83±1.8 vs. 2.08±1.2 pg/mL; p=0.582). Correlation analysis showed significant association among Adp and NT-proBNP levels, (r=0.448; p<0.001), and left ventricular ejection fraction (LVEF) values (r=-0.466; p<0.001). The Adp and NT-proBNP showed comparable diagnostic performances with mean [95% confidence interval] areas under the curves of 0.857 (0.771-0.944) and 0.888 (0.815-0.960), respectively.

**Conclusion:** There were significant correlation between Adp levels with NT-proBNP levels and LVEF values but no any association between Adp levels with body mass index values and TNF-α levels in patients with newly diagnosed systolic heart failure. The result may arouse suspicion about the hypothesis, which proposes that Adp levels simply reflects disease severity or cardiac cachexia in patients with HF.
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**Key words:** Heart failure, adiponectin, NT-ProBNP, cardiac cachexia, diagnostic accuracy

## ÖZET

**Amaç:** Kalp yetmezliği (KY) olgularında NT-pro-beyin natriüretik peptid'in (NT-proBNP) tanısal değeri bilinmektedir. Adiponektin (Adp) düzeyleri bu olgularda yükselmektedir, ancak tanısal değeri henüz belirsizdir. Çalışma, yeni tanı almış, kaşektik olmayan sistolik kalp yetmezlikli olgularda söz konusu serum göstergelerinin muhtemel ilişkisinin araştırılması için tasarlanmıştır.

**Yöntemler:** Sistolik KY tanısı konan 57 olgu ile yaş-cinsiyet uyumlu 20 kontrol olgusu gözlemsel kesitsel çalışmaya dahil edildi. Fizik muayene ve ekokardiyografik değerlendirmenin yanı sıra serum Adp, NT-proBNP, tümör nekrozis faktör-alfa (TNF-α) düzeyleri ölçüldü. Çalışma değişkenleri gruplar arasında karşılaştırıldı. Korelasyon analizleri yapıldı ve göstergelerin tanısal geçerliliği ROC analizi ile karşılaştırıldı.

**Bulgular:** Adp ve NT-proBNP düzeyleri KY grubunda anlamlı şekilde yüksek bulundu (sırasıyla 20.19±12.9'e karşılık 7.65±4.6 µg/mL; p<0.001 ve 1051.74±606.2'e karşılık 222.53±65.6 pg/mL; p=0.002). TNF-α düzeyleri her iki grupta benzerdi (2.83±1.8 vs. 2.08±1.2 pg/mL; p=0.582). Korelasyon analizi Adp ile NT-proBNP düzeyleri (r=0.448; p<0.001) ve Adp ile sol ventriküler ejeksiyon fraksiyon (SVEF) değerleri arasında anlamlı korelasyon

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olduğunu gösterdi (r=-0.466; p<0.001). ROC analizi ile Adp ve NT-proBNP seviyelerinin karşılaştırılabilir tanısal değere sahip olduğu saptandı: Eğri altında kalan alanlar sırası ile 0.857 (%95 GA; 0.771-0.944 ) ve 0.888 (%95 GA; 0.815-0.960) bulundu.
**Sonuç:** Yeni tanı almış sistolik kalp yetmezlikli olgularda Adp seviyeleri ile NT-proBNP ve SVEF arasında anlamlı korelasyon mevcut iken; Adp ile beden kitle indeksi ve TNF-α düzeyleri arasında herhangi bir ilişki saptanmamıştır. Bu sonuç Adp seviyelerinin KY olgularında ilerlemiş hastalığın veya kardiyak kaşeksinin bir göstergesi olduğu hipotezi ile çelişmektedir. *(Anadolu Kardiyol Derg 2013; 13: 221-6)*
**Anahtar kelimeler:** Kalp yetmezliği, adiponektin, NT-ProBNP, kardiyak kaşeksi, tanısal duyarlılık

## Introduction

As more patients are diagnosed with heart failure (HF) each year, HF management has become a growing public health issue. Biomarkers, such as natriuretic peptides, offer consistent and cost-effective means of monitoring response to therapy. Considering that, HF is a systemic disease, biomarkers reflecting cardiac and systemic abnormalities in HF may add incremental diagnostic and/or prognostic information to natriuretic peptides. There is a growing interest in using newer biomarkers to obtain pathophysiological insight into and, possibly, to improve the management of HF.

Adiponectin (Adp) is an anti-inflammatory, insulin-sensitizing, and anti-atherogenic adipocytokine, which plays a fundamental role in energy homeostasis (1). Adp comprises 244 amino acids, and it is synthesized and secreted in large quantities from adipose tissue (1, 2). Paradoxically given its origin, circulating levels of Adp correlate inversely with body weight and body mass index (BMI), possibly as the result of a negative feedback interaction between the hormone and adipose tissue. It is well documented that high levels of circulating Adp have a favorable effect on metabolic processes and protect against derangements that lead to obesity, metabolic syndrome, atherosclerosis, and subsequent cardiovascular disease (2, 3). Epidemiological studies have shown that low Adp levels correlate with an increased risk of cardiovascular disease in obese individuals, in subjects with insulin resistance and in diabetes (2-5).

However, a paradoxical increase in Adp levels is observed in patients with systolic HF. Higher plasma concentrations of the hormone are associated with worse prognosis in HF, in contrast to what is seen in obese or diabetic patients (6-8). It is therefore not clear whether Adp is involved in the pathogenesis of HF or simply reflects the activation of complex and opposing maladaptive mechanisms. As a possible mechanism, previous studies proposed that in end-stage HF, wasting with the loss of adipose tissue (cardiac cachexia) might lead to increased levels of Adp (7, 9, 10). The mechanism raised suspicions about diagnostic values of Adp levels in HF patients without cardiac cachexia.

We, therefore, sought to investigate the Adp levels and its possible association with natriuretic peptide levels and left ventricular function in a cohort of non-cachectic patients with newly diagnosed systolic HF.

## Methods

### Study design

The current study has an observational cross-sectional design.

### Study population

Our population is represented by a total of 57 consecutive patients with HF who were admitted to outpatient cardiology clinic of the Central Hospital between January and June 2009. All patients fulfilled the following inclusion criteria: I. Clinical congestive HF defined by Framingham criteria (11), II. Left ventricular (LV) systolic dysfunction (LV ejection fraction <35%) documented by echocardiography, III. New York Heart Association (NYHA) functional capacity class 3-4.

This study also enrolled age- and sex-matched 20 control subjects without obvious heart disease who underwent cardiac catheterization for atypical chest pain in our hospital during the same enrollment period.

Patients were excluded if they had hemodynamically significant obstructive valvular disease, cor pulmonale, myocarditis, constrictive pericarditis, congenital heart disease, renal dysfunction (serum creatinine concentration >2.5 mg/dL), or if they had experienced myocardial infarction or unstable angina within the last 4 months.

Written informed consent was obtained from all patients with HF and control subjects prior to enrollment. The study was performed in accordance with the principles stated in the Declaration of Helsinki and approved by the Local Ethics Committee.

### Study protocol and definitions

All demographic and clinical features were collected from medical history of the patients. Baseline examination included a questionnaire involving gender, age and smoking status. BMI value was calculated as the ratio of the weight in kilograms to the height in squared meters. Hypertension was defined as systolic pressure >140 mmHg and/or diastolic pressure was >90 mmHg or if the individual was taking antihypertensive medications (12). The diagnosis of diabetes was based on previous history of diabetes treated with or without drug therapies (12). Hyperlipidemia was defined by elevated total plasma cholesterol levels (>200 mg/dL) (12).

The medical history was obtained to document the etiology and the severity of HF symptoms according to the NYHA functional class. An ischemic etiology was defined by a history of myocardial infarction (electrocardiographic findings or positive troponin levels) and/or positive results from a noninvasive stress test or cardiac catheterization. Evidence-based therapy for systolic HF was started to HF patients.

We analyzed clinical, echocardiographic and laboratory parameters between the study groups and also investigated possible relationship between Adp, natriuretic peptide levels and left ventricular function.

**Study variables**

The following demographic, clinical, echocardiographic variables were evaluated: age, gender, weight, waist circumference, body mass index, smoking status, prevalence of diabetes mellitus, hypertension, hyperlipidemia, LV ejection fraction, LV fractional shortening, levels of NT-pro-brain natriuretic peptide (NT-proBNP), tissue necrosis factor alpha (TNF-$\alpha$) and Adp. Primary end-point of the study was investigating the Adp levels and its possible association with natriuretic peptide levels and left ventricular function in a cohort of newly diagnosed systolic HF. The diagnosis of systolic HF was established as clinically defined by Framingham criteria (11) and confirmed by echocardiographic examination (LV ejection fraction <35%).

**Echocardiography**

Two-dimensional and Doppler echocardiographic examinations (Philips EnVisor C, Andover MA, USA) were performed and analyzed in a blinded manner. Measurements of the systolic and diastolic chamber dimensions and wall thickness were obtained from 2-dimensional imaging according to the recommendations of the American Society of Echocardiography (13). Left ventricular ejection fraction (LVEF) was measured by Simpson's modified biplane method (13). LV fractional shortening (FS) was calculated from the M-mode using the following equation:

FS (%): [(LVIDD-LVIDS)/LVIDD] x 100

**Laboratory analyses**

Venous blood samples were drawn at admission. Whole blood was collected in non-heparinized tubes and centrifuged at 1750 g for 10 minutes at 4°C. The obtained serum samples were stored at -20°C until they were assayed.

Serum Adp concentrations (µg/mL) were determined by a commercially available enzyme-linked immunosorbent assays (ELISA) kit (Biovendor, Heidelberg, Germany). The detection limit reported is 0.2 µg/mL. The antibodies used in this ELISA are specific for human adiponectin. No cross reactivity has been observed for human leptin, leptin receptor and resistin at 100 ng/mL. The intra-assay coefficient of variation measured was 5.9% and the inter-assay coefficient of variation was 6.3%.

NT-proBNP (pg/mL) was measured in plasma samples using commercially available kits from Biomedica (Vienna, Austria) with the intra- and inter-assay variation coefficient was 6% and 8%, respectively.

Serum TNF-$\alpha$ (pg/mL) was measured by a highly sensitive ELISA in a commercially available kit (Bender MedSystems, Vienna, Austria), with intra- and inter-assay coefficients of variation of 8.5% and 9.8%, respectively. The limit of detection was determined to be 0.13 pg/mL.

**Statistical analysis**

Statistical analysis was performed with the use of SPSS Statistics version 15.0. (SPSS, Inc., Chicago, IL, USA). Quantitative variables are expressed as mean±standard deviation (SD), and qualitative variables as percentages. Continuous variables were compared between the two groups using Mann-Whitney U test, whereas proportions were compared by Fisher's exact test. Correlation analyses were done by Spearman's test. Receiver operating characteristic (ROC) analysis was used to assess the diagnostic validity of the markers, and areas under the ROC curve (AUC) were compared. All results were considered statistically significant at the level of $p<0.05$.

## Results

**Clinical characteristics**

All HF patients had NYHA III or IV functional class at enrollment. Twenty-eight patients (49%) had ischemic etiology in HF group. Clinical characteristics of patients with HF and control subjects are shown in Table 1. Waist circumference was significantly higher in patients with HF than in control subjects (95.8±10.8 vs. 87±12 cm; p=0.015; respectively).

**Levels of biomarkers**

Adp and NT-proBNP levels were significantly higher in HF group than in control group (20.19±12.9 vs. 7.65±4.6 µg/mL; p<0.001 and 1051.74±606.2 vs. 222.53±65.6 pg/mL; p=0.002; respectively). However TNF-$\alpha$ levels were similar between the groups (2.83±1.8 vs. 2.08±1.2 pg/mL; p=0.582; respectively). Biomarker levels of the study groups are shown in Table 1.

**Table 1. Clinical characteristics and biomarker levels of the study population**

| Variables | Patients with HF (n=57) | Control subjects (n=20) | *p |
|---|---|---|---|
| Age, years | 63.6±11.5 | 60.8±9.5 | n.s |
| Male gender, % | 73 | 55 | n.s |
| Weight, kg | 79.7±10.5 | 81.6±10.2 | n.s |
| Waist circumference, cm | 95.8±10.8 | 87±12 | 0.015 |
| Body mass index, kg/m$^2$ | 26.6±4.3 | 30.5±4.9 | n.s |
| Diabetes mellitus, % | 15.7 | 20 | n.s |
| Hypertension, % | 40.3 | 35 | n.s |
| Smoking, % | 35.1 | 40 | n.s |
| Hyperlipidemia, % | 40.3 | 50 | n.s |
| LVEF, % | 24.2±4.7 | 57.9±2.6 | <0.001 |
| LVFS, % | 17±5 | 39±4 | <0.001 |
| Adiponectin, µg/mL | 20.19±12.9 | 7.65±4.6 | <0.001 |
| NT-proBNP, pg/mL | 1051.74±606.2 | 222.53±65.6 | 0.002 |
| TNF-$\alpha$, pg/mL | 2.83±1.8 | 2.08±1.2 | n.s |

* Quantitative variables as mean ± standard deviation were compared by Mann-Whitney U test, **Qualitative variables as proportions were compared by Fisher's exact test.
HF - heart failure, LVEF - left ventricular ejection fraction, LVFS - left ventricular fractional shortening, NT-proBNP - N terminal-probrain natriuretic peptide, TNF-$\alpha$ - tumor necrosis factor-alpha

**Table 2. The relationships of adiponectin levels with clinical, echocardiographic variables and other biomarkers in patients with systolic HF**

| Variables | Adiponectin, µg/mL | |
|---|---|---|
| | *r | *p |
| Age, years | 0.173 | 0.134 |
| Body mass index, kg/m$^2$ | -0.110 | 0.417 |
| LVedd, mm | 0.291 | 0.01 |
| LVesd, mm | 0.424 | <0.001 |
| LAd, mm | 0.170 | 0.139 |
| IVS, mm | -0.221 | 0.053 |
| PW, mm | -0.112 | 0.331 |
| LVEF, % | -0.466 | <0.001 |
| LVFS, % | -0.470 | <0.001 |
| NT-proBNP, pg/mL | 0.448 | <0.001 |
| TNF-α, pg/mL | 0.114 | 0.326 |

*Pearson correlation analysis
HF - heart failure, IVS - interventricular septum, LAd - left atrial diameter, LVedd - left ventricular end-diastolic diameter, LVesd - left ventricular end-systolic diameter, LVEF - left ventricular ejection fraction, LVFS - left ventricular fractional shortening, NT-proBNP - N- terminal-proBrain natriuretic peptide, PW - posterior wall, TNF-α - tumor necrosis factor-alpha

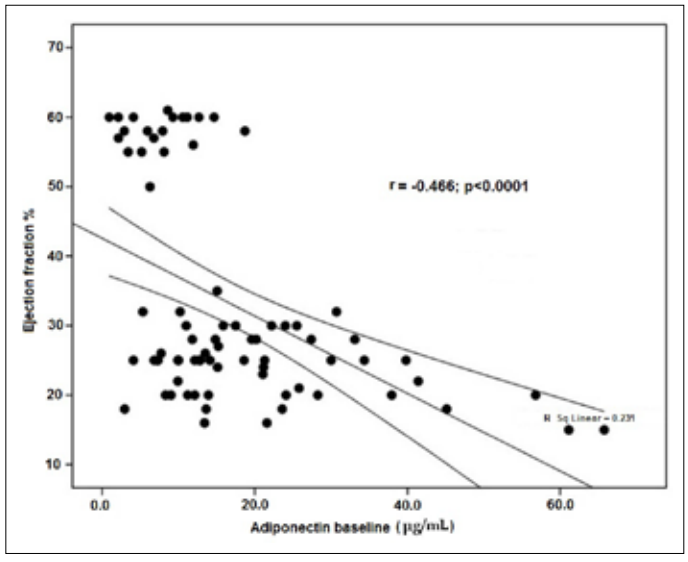


**Figure 1. The relationship between serum adiponectin levels and LVEF values in patients with systolic heart failure**
LVEF - left ventricular ejection fraction

### Associations of Adp and other study variables

Correlation analysis showed positive association among Adp and NT-proBNP levels (r=0.448; p<0.001), LV end-diastolic (r=0.291; p=0.01), end-systolic diameters (r=0.424; p<0.001) and LV fractional shortening (r=-0.470; p<0.001) (Table 2). Furthermore, significant negative correlations were found between the LVEF and serum Adp (Fig. 1) and NT-proBNP levels (r=-0.466; p<0.001 and r=-0.552; p<0.001; respectively), but there was no any significant correlation between LVEF and TNF-α levels (r=-0.73; p=0.527). There was no any association between levels of Adp, NT-ProBNP and TNF-α in control subjects. Serum Adp was not correlated with BMI in both patients and control subjects groups.

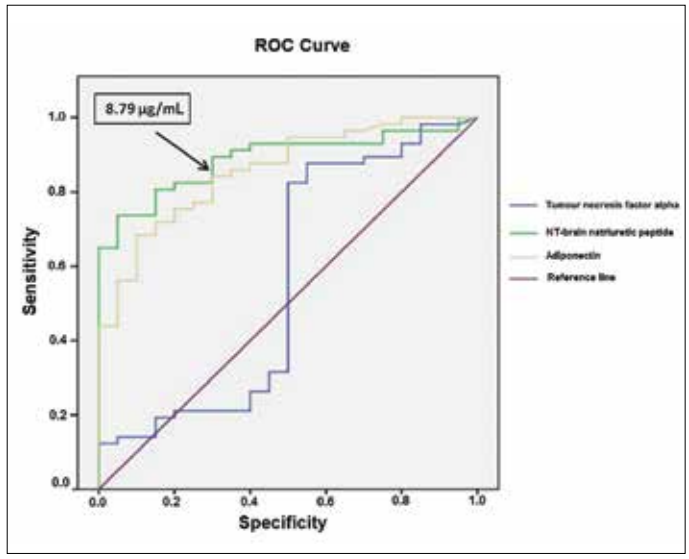


**Figure 2. ROC curves comparing the diagnostic performances of serum NT-proBNP, Adp and TNF-α level for identifying patients with heart failure. Adp and NT-proBNP showed comparable diagnostic performances with mean AUC of 0.857 (95% CI 0.771-0.944) and 0.888 (95% CI 0.815-0.960), respectively. Diagnostic performance of TNF-α levels were not statistically significant. [AUC: 0.557 (95% CI: 0.338-0.727), p=0.447] Optimum cut-off value of serum Adp level is shown**
Adp - adiponectin, NT-proBNP - NT-pro-brain natriuretic peptide, TNF-α - tissue necrosis factor alpha

In patients with systolic HF, the Adp and NT-proBNP showed comparable diagnostic performances (Fig. 2) with mean [95% confidence interval (CI)] areas under the curves (AUC) of 0.857 (0.771-0.944, p<0.001) and 0.888 (0.815-0.960, p<0.001), respectively. At the optimal cut off value of 8.79 µg/mL for Adp, sensitivity was 86% and specificity of 65% for predicting the presence of HF.

## Discussion

In this study, we sought to investigate the Adp levels and its possible association with natriuretic peptide levels and left ventricular function in a cohort of non-cachectic patients with newly diagnosed untreated systolic HF. Our study has demonstrated that serum Adp levels were significantly increased in this population. Heart failure group of the study was selected meticulously and they had unique clinical characteristics. They were unaware that they had HF before the enrollment; the first hospital admission date due to HF symptoms of them was study enrollment time. Consequently, HF patients of the study had normal or overweight BMI ratios which confirming to exclude the cachectic HF patients from the study. The mean BMI was 26.66±4.3 in patients with HF.

Previous studies concluded that Adp may be a marker of muscle wasting in HF and it levels are elevated in patients with cardiac cachexia (3, 9, 10). Kung et al. (14) asserted that elevated Adp levels were significantly associated with advanced disease

state and metabolic impairment. However, Adp levels were elevated in our HF group which had recently diagnosed and more reflective of early steps of metabolic disturbances due to HF.

The role of Adp in HF is controversial. Theoretically, progression of HF is closely associated with a reduction in total body weight as part of a wasting process. This decrease in body weight will result in an increase in Adp levels. Elevated Adp levels may compensate a state of impaired energy metabolic efficacy (a progressive shift from fatty acid utilization to glucose utilization) and malnutrition (15). Hence, functional adiponectin resistance has been observed in the skeletal muscle of patients with chronic HF (16). This would explain why, despite known cardiac and vascular protective effects (4). Adp is paradoxically associated with increased mortality in HF (2, 4, 8, 10). However, the hypothesis which asserts that the increased Adp levels is a marker of the advanced disease state and metabolic disturbances is controversial, because in our study, Adp levels were also increased in the HF population with non-cachectic patients. Adp is mainly expressed in adipose tissue; serum adiponectin level correlates negatively with BMI in stable CHF (2, 3, 10). In our study population, serum adiponectin concentrations were not correlated with BMI or waist circumference. Although the patients with HF had greater waist circumference than in control subjects, this may be as a result of hepatic or fluid congestion. Thus, major sources of circulating Adp are not thought to be adipose tissue in our HF population. Heart failure patients of the study were enrolled at the first hospital admission time due to HF symptoms and all of them at first days of stage C- HF. Recent studies have shown that Adp mRNA and protein are expressed in cardiomyocytes of rodents and humans and immunoreactive Adp was found in the myocardial tissues obtained from the autopsied heart (17-19). Takano et al. (20) showed significant transcardiac gradient of Adp levels in patients with HF. Adp may be released from the heart in patients with HF and the amount of heart-originated Adp may constituted significant part of serum levels. We have no data about the source of Adp in the present study.

The factors controlling Adp secretion in HF are still poorly understood and remain controversial. It is possible that increased proinflammatory cytokines may stimulate Adp secretion. Previous studies have proposed that TNF-$\alpha$ has been suggested to increase Adp secretion, although this literature is conflicting (21, 22). Heart failure population of the study had normal TNF-$\alpha$ levels and we did not find any relationship between serum Adp and TNF-$\alpha$ levels which supporting these conflicted results. However, our study demonstrated that serum Adp levels correlated positively with LVEF values and serum NT-proBNP levels. Takano et al. (20) proposed that Adp is released from the heart into the circulation in proportion to the severity of LV dysfunction in patients with HF irrespective of etiologies of HF. Accordingly; heart-originated Adp may at least partly contribute to the increased levels of Adp seen in patients with HF who had severe LV systolic dysfunction and normal BMI such as the study HF population.

Previous studies showed strong correlation between Adp and natriuretic peptide levels (20, 23). Whether the correlation between two markers simply reflects a parallel evolution of two biomarkers that mirror disease severity, or whether there is a causal association remains to be further explored. Moro et al. shown that atrial natriuretic peptide directly stimulates Adp production in adipocytes cultured under lipolysis inhibition (24). Thus, atrial natriuretic peptide and BNP, whose levels are increased in HF, might possibly stimulate adiponectin secretion resulting in increased adiponectin levels in patients with HF. Indeed, Tsukamoto et al. (25) demonstrated that natriuretic peptides increase the production of Adp by human adipocytes.

### Study limitations

There are several limitations of the current study. First, the design was observational cross-sectional and measurements of serum biomarkers, BMI and LVEF values were performed at the same visit. The study was a single-center study performed in a relatively small sample of patients and restricted to Caucasian patients only. We measured Adp levels in peripheral venous samples, but not in coronary sinus samples. We were unable to determine transcardiac gradient of Adp. The assay used in our study measured total Adp levels and we have no data about the source of Adp. We were therefore unable to distinguish between the low molecular weight and the high molecular weight form. Finally, our study is not a diagnostic accuracy study; however, we found that Adp levels displayed to comparable diagnostic performance with NT-proBNP for diagnosis of systolic HF. Therefore, further studies are needed to explore its validity.

## Conclusion

Major findings of our study were the presence of significant correlation between Adp levels with, NT-proBNP levels and LVEF values, but absence of any association between Adp levels with body mass index values and TNF-$\alpha$ levels in patients with newly diagnosed systolic heart failure. The result may arouse suspicion about the hypothesis, which proposes that Adp levels simply reflects disease severity or cardiac cachexia in patients with HF.

**Conflict of interest:** None declared.

**Peer-review:** Externally peer-reviewed.

**Authorship contributions:** Concept - İ.T., U.Ö.T., E.A.; Design - U.Ö.T.; Supervision - E.E., E.A.; Materials - B.K., G.S.T.; Data collection &/or Processing - B.K., N.T., U.Ö.T., İ.T.; Analysis &/or interpretation - E.E., U.T., Literature search - N.T., E.A.; Writing - U.Ö.T., G.S.T.; Critical review - G.S.T., İ.T., E.E.

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