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Original Article

Importance of Diastolic Dysfunction and Nt-ProBNP Measurement for Identification of Volume Load in Predialysis Chronic Renal Failure Patients

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ABSTRACT

Objective: Volume excess is frequently observed in chronic kidney disease (CKD) patients and over time may induce diastolic dysfunction and its continuation of cardiac failure. It was aimed to identify the correlation between E/e' ratio, entering use in recent times and associated with left ventricle filling pressure, and NT-proB-type natriuretic peptide (proBNP), a substantial indicator in heart failure.

Methods: The study included 44 euvolemic CKD patients with preserved left ventricular ejection fraction and without cardiovascular disease (25 women, 19 men) and 26 healthy controls (15 women, 11 men). NT-proBNP levels were measured with the ELISA method and all participants were assessed with transthoracic conventional Doppler and tissue Doppler echocardiography to examine the relationship between NT-proBNP values with E/e' ratio which is the peak early diastolic mitral rate to peak early diastolic mitral annular velocity.

Results: The patient group comprised 25 women (56.8%) and 19 men (43.2%) and the mean age was 59.36±9.26 years. Healthy controls comprised 15 women (57.7%) and 11 men (4.23%) with mean age of 56.58±10.39 years. NT-proBNP measurements and E/e' ratios were concluded to be higher in the patient group compared to the control group ($p<0.001$). Taking cutoff value of 300 pg/mL for NT-proBNP as the basis, the sensitivity was 53.66% and specificity was 100%. With E/e' cut-off value of 15, the sensitivity was 86.36% and specificity was identified as 73.08%.

Conclusion: In our study, NT-proBNP and E/e' values were identified to be important parameters for the prediction of diastolic dysfunction in chronic renal failure patients without clinical findings of heart failure. Larger, extensive, comprehensive, and prospective studies investigating this issue are necessary to confirm the value and usefulness of both NT-proBNP and the E/e' ratio in clinical practice.

INTRODUCTION

Cardiovascular disease (CVD) is the most main cause of morbidity and mortality among chronic kidney disease (CKD) patients. CKD patients frequently have the classic risk factors identified for CVD such as diabetes mellitus, advanced age, dyslipidemia, fluid volume excess, and hypertension. Recent studies have shown a correlation between a renal function with cardiac failure risk for a broad range of diseases from preclinical renal disease to advanced CKD.[1]

Of late years, plasma biomarkers, especially natriuretic peptides, and echocardiographic investigations are recommended to determine patients with high cardiovascular

risk. Studies have associated natriuretic peptides with an independent prediction of present and expected CVD. Pro-B-type natriuretic peptide (proBNP) is a diuretic peptide synthesized in the ventricular myocardium and released into plasma affecting intraventricular volume, wall tension, and diastolic end pressure.[2] CVD is seen more frequently associated with CKD and has a poorer prognosis compared to the general population. Left ventricular systolic and diastolic dysfunction, left ventricular mass, and vascular calcification are among the markers of increased cardiovascular risk in diastolic dysfunction that have been shown in many studies to be independent predictors of mortality. Volume excess is often seen in CKD patients and over time causes diastolic dysfunction and heart failure. As a result, identifying and management of volume status is important.

Diastolic dysfunction is a tableau characterized by preserved left ventricular systolic end pressure, but with inadequate left ventricular filling as filling pressure does not increase. Renal failure patients with left ventricle hypertrophy (LVH) frequently have left ventricular diastolic dysfunction.[3] E/e' ratio is a parameter associated with left ventricle filling pressure and values of 15 and above indicate increased filling pressure and increased left atrium pressure.[4] The E/e' ratio was defined as an important prognostic marker in many CVDs such as systolic or diastolic heart failure, LVH, myocardial infarction, and subclinical myocardial disease.[5]

A study comparing NT-proBNP with BNP among symptomatic and asymptomatic heart failure patients based on NT-proBNP was an important marker of asymptomatic heart failure.[6] In the PRIDE study and for patients attending with shortness of breath complaints, NT-proBNP had a diagnostic value and 300 pg/mL NT-proBNP was determined as a cutoff value to exclude heart failure. In general, BNP <100 pg/mL is used to exclude heart failure diagnosis, with values >500 pg/mL as the cutoff value to support diagnosis. Similarly, NT-proBNP values of <300 pg/mL and >450 pg/mL (>900 pg/mL for patients over 50 years) were determined as cutoff values.[7]

In our study, we aimed to research the correlation of the E/e' ratio, the echocardiographic finding of diastolic dysfunction, with NT-proBNP in patients with CKD but no clinical findings of heart failure and identify the value of their use to identify volume status.

MATERIALS AND METHODS

Study population

This prospective clinical study contained 44 patients with CKD with no dialysis story (25 women, 19 men) attending to our internal medicine clinic and 26 healthy controls (15 women, 11 men). Patients with coronary artery disease, atrial fibrillation, valve disease, acute renal failure, active infection, and malignancy were excluded from the study. The presence of CKD was described as GFR reduction (<60 mL/min/1.73 m^2) lasting 3 months or longer or pathological abnormalities defined as structural or functional abnormalities of the kidney lasting longer than 3 months with or without GFR reduction or abnormalities on blood (blood test results in other situations such as multiple myeloma, systemic vasculitis, low calcium/high phosphorus and parathormone [PTH] plasma levels, etc.), urine or imaging tests (single kidney, polycystic kidney, findings leading to consideration of chronic disease due to kidney dimensions or parenchyma thickness).

Laboratory assessment

Fasting blood glucose, creatinine, urea, uric acid, sodium (Na^+), potassium (K^+), calcium (Ca^{++}), phosphorus (PO_4), PTH, HbA1c, albumin, total cholesterol, triglyceride, LDL, HDL, CRP, 25(OH) D vitamin levels were measured, along with spot urine protein/creatinine (mg/g) ratio in first-morning urination. The enzymatic colorimetric method (COBAS311, Roche Diagnostics GmbH, Mannheim, Germany) was used to determine the serum cholesterol, triglycerides, and HDL levels. Fridewald formula was used to calculate LDL. Moreover, the hexokinase method (Roche Diagnostics GmbH, Mannheim, Germany) which uses the enzymatic route was performed to measure the serum glucose. The CKD-EPI method was used to calculate the estimated GFR (eGFR).

In addition to these tests, the NT-proBNP level was examined by placing blood in 1 plain biochemistry tube, centrifuging for 10 min at 4000 rpm in the biochemistry laboratory and storing in a freezer. The stored samples were studied with a BT-LAB Human NT-proBNP ELISA kit. NT-proBNP is influenced by some factors such as age, volume status, and water-salt metabolism, so the cutoff value of 300 pg/mL was used with the information that <300 pg/mL strongly excluded heart failure in all age groups.[7]

Echocardiographic assessment

All the patients in the study had echocardiographic assessments performed by the same cardiologist with a GE Vivid S60 device in our hospital's cardiology clinic. Measurements used a 2.5 mHz probe (GS3S). With transthoracic echocardiography, left ventricle ejection fraction (EF), left atrium, septum, and posterior wall thicknesses, and left ventricular diastolic end volume (LVEDV) were examined. To evaluate the diastolic function of the left ventricle, conventional Doppler echocardiography was used to measure the mitral flow parameters of mitral valve early fill rate (E) and late diastolic flow (A), and tissue Doppler echocardiography was used to measure mitral annulus early velocity (e'). The E/A and E/e' ratios were calculated. The value of 15 was taken as E/e' cutoff value as stated in a few studies.[5,8]

Statistical analysis

In our study, continuous variables are defined with descriptive statistics (mean, standard deviation). Comparison of two independent variables that did not show normal distribution was made using the Mann-Whitney U test. Student's test was used when comparing two in-

dependent variables with normal distribution. Receiver operating characteristic analysis was used with the aim of calculating the cutoff points and area under the curve. To investigate the correlation between categoric variables, the Chi-square or where appropriate Fisher's exact test was used. Analyzes were performed using MedCalc Statistical Software version. 12.7.7 (MedCalcSoftw.bvba, Ostend, Belgium; http://www.medcalc.org; 2013).

RESULTS

The study enclosed a total of 44 patients and 26 healthy controls. The patient group included 25 women (56.8%) and 19 men (43.2%) with a mean age of 59.36±9.26 years. The healthy control group contained 15 women (57.7%) and 11 men (42.3%) with a mean age of 56.58±10.39 years. Statistically significant differences were found for the distributions of E/e', NT-pro-BNP, e', A, EF, septum thickness, posterior wall thickness, E/A, LA diameter, systolic and diastolic blood pressures, BMI, height, creatinine, GFR, urea, uric acid, PTH, Hgb, triglyceride, spot urine protein/creatinine ratio (mg/g), HbA1c ($p<0.001$); K^+, and CRP ($p=0.001$) (Tables 1 and 2).

For disease cutoff, NT-proBNP ($p<0.001$) and E/e' ($p<0.001$) were each identified as important parameters. NT-proBNP above 95.55 and E/e' above 9 may be associated with the presence of disease. Based on cutoff value of 300 pg/mL for NT-proBNP, sensitivity was calculated as 53.66% and specificity was identified as 100%. Based on cutoff value of 15 for E/e', sensitivity was 86.36% and specificity was 73.08% (Table 3, Figs. 1 and 2).

To determine the relationship between NT-pro-BNP, E/e', and other parameters, Spearman correlation analysis was performed. As shown in Table 4, positive correlations with NT-proBNP were observed with age ($r=0.456$, $p=0.003$) and PTH ($r=0.445$, $p=0.004$). There were negative correlations identified between NT-proBNP and GFR ($r=-0.345$, $p=0.022$), and albumin ($r=-0.492$, $p=0.001$). Negative correlations were established between E/e' and GFR ($r=-0.383$, $p=0.013$) and albumin ($r=-0.346$, $p=0.021$). The positive correlations were identified between E/e' and age ($r=0.361$, $p=0.016$), phosphorus ($r=0.378$, $p=0.012$), and proteinuria ($r=0.301$, $p=0.047$) (Table 4).

DISCUSSION

CVDs are the primary cause of mortality in CKD patients and many studies have proposed that CVD in CKD begins firstly with diastolic dysfunction and then later transforms into progressive fibrosis and ventricle hypertrophy. For this reason, aggressive intervention in the early stage may prohibit irreversible cardiac remodeling and the associated poor prognosis. As a result, there is a need for simple clinical assessments to identify diastolic dysfunction in the early stage.[9,10]

The volume load and increased pressure formed by loss of renal function and reduction or complete loss of diuresis in CKD patients begin remodeling in the left ventricle. Diastolic dysfunction may be observed as a result of the increase in left ventricle diameter and volume, and later

Table 1. Comparison of parameters according to group (cardiovascular disease vs. healthy individuals)

	Control (n=26)		Patient (n=44)		p
	n	%	n	%	
Sex					
Male	11	42.3	19	43.2	0.95
Female	15	57.7	25	56.8	
ACEI					
No	26	100.0	37	84.1	0.041
Yes	0	0.0	7	15.9	
ARB					
No	26	100.0	42	95.5	0.526
Yes	0	0.0	2	4.5	
Loop diuretic					
No	26	100.0	36	81.8	0.022
Yes	0	0.0	8	18.2	
Thiazide					
No	26	100.0	43	97.7	1.000
Yes	0	0.0	1	2.3	
ACEI+thiazide					
No	26	100.0	36	81.8	0.022
Yes	0	0.0	8	18.2	
ARB+thiazide					
No	26	100.0	34	77.3	0.010
Yes	0	0.0	10	22.7	
BB					
No	26	100.0	32	72.7	0.002
Yes	0	0.0	12	27.3	
BB+thiazide					
No	26	100.0	43	97.7	1.000
Yes	0	0.0	1	2.3	
CCB					
No	26	100.0	25	56.8	<0.001
Yes	0	0.0	19	43.2	
Alpha blocker					
No	26	100.0	36	81.8	0.022
Yes	0	0.0	8	18.2	
Statin					
No	26	100.0	33	75.0	0.005
Yes	0	0.0	11	25.0	
GFR					
Less than 30	0	0.0	10	22.7	0.064
30–45	0	0.0	19	43.2	
45–60	0	0.0	15	34.1	
E/e'					
Less than 15	25	96.2	28	63.6	0.002
15 and higher	1	3.8	16	36.4	

*Fisher's Exact test; ACEI: Angiotensin-converting enzyme blocker; ARB: Angiotensin II receptor blocker; BB: Beta blocker; CCB: Calcium channel blocker.

Table 2. Comparison of parameters between groups (cardiovascular disease vs. healthy individuals)

	Control (n=26)	Patient (n=44)	P
Age	58.58±10.39	59.36±9.26	0.058
SBP	121.92±8.38	145.68±14.89	<0.001
DBP	74.42±4.54	90.8±13.47	<0.001
BMI (kg/m^2)	24.53±2.27	26.91±2.68	<0.001*
Creatinine	0.77±0.14	1.74±0.58	<0.001
GFR, CKD-EPI	95.42±27.18	37.34±11.76	<0.001
Urea	29.88±8.91	65.02±27.56	<0.001
Uric acid	4.97±1.49	6.51±1.86	0.001*
Albumin	3.96±0.24	3.79±0.41	0.055*
Na^+	139.04±2.07	136.57±14.89	0.746
K^+	4.2±0.34	4.68±0.63	0.001*
Ca^{++}	9.5±0.43	9.27±0.77	0.061
PO_4	3.26±0.5	3.61±1.02	0.275
PTH	57.23±21.69	133.45±127.05	<0.001
25(OH)D	16.12±9.8	19.98±31.26	0.609
LDL	109.54±32.98	121±44.08	0.576
HDL	46±7.95	47.32±11.32	0.780
TG	114.62±40.83	189.02±86.63	<0.001
Total cholesterol	183.08±37.34	197.41±62.74	0.294*
Hgb	13.78±1.63	11.68±2.07	<0.001
CRP	2.39±1.31	4.55±3.39	0.001
Spot urine prot/cr (mg/g)	80.46±30.73	790.5±1227.55	<0.001
HbA1c	5.67±0.43	8.04±2.45	<0.001
NT-proBNP	41.45±24.19	296.46±333.23	<0.001
E	0.83±0.16	0.76±0.21	0.119
E'	0.1±0.03	0.06±0.02	<0.001
E/e'	11.14±14.2	14.69±6.22	<0.001
A	0.55±0.1	0.88±0.2	<0.001
E/A	1.55±0.38	0.93±0.42	<0.001
EF	64.62±1.96	61.36±4.49	<0.001
LVEDV	4.49±0.39	4.64±0.7	0.652
LVESV	2.8±0.34	12.2±60.9	0.055
Septum	1.04±0.15	1.27±0.22	<0.001
Posterior wall	1.02±0.12	1.22±0.18	<0.001
LA	3.3±0.46	3.8±0.58	<0.001*
AA	2.98±0.4	3.09±0.35	0.213*
Aorta Vmax	1.19±0.19	1.33±0.25	0.016

*Mann-Whitney U test, *Student-t test. SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index; EF: Ejection fraction; LVEDV: Left ventricular end-diastolic volume; LVESV: Left ventricular end-systolic volume; LA: Left atrium; AA: Ascendant aorta.

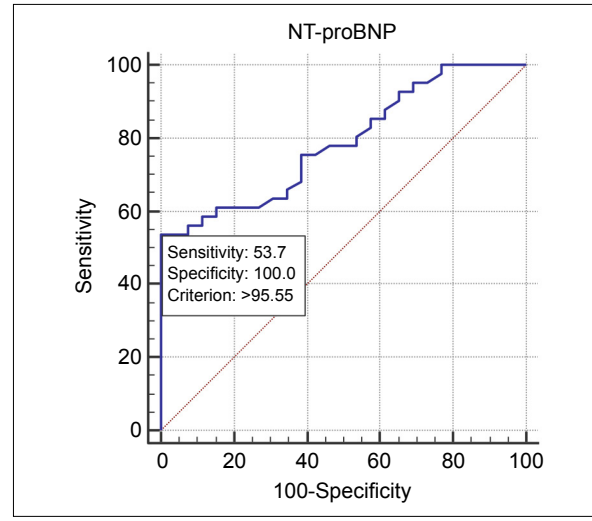

Figure 1. The area under the curve as a result of receiver operating characteristic analysis to identify cutoff point for NT-type natriuretic peptide.

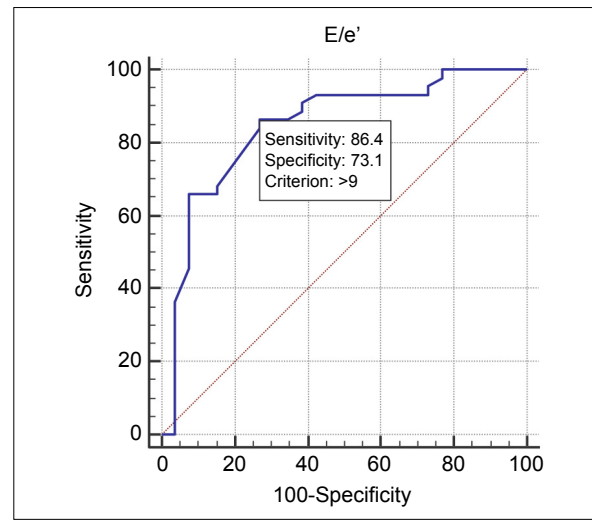

Figure 2. The area under the curve as a result of receiver operating characteristic analysis to identify cutoff point for E/e'.

forming myocardial fibrosis and LVH. Diastolic dysfunction is observed at higher rates in CKD compared to the normal population.[11] In recent times, Doppler echocardiographic imaging has begun to be used to evaluate diastolic function. The e' rate is an index independent of the relative load of LV relaxation and the mitral E/e' ratio was stated to show good correlation with LV filling pressures.[12] In our study, E/e' values were identified to be elevated in the patient group compared to the control group (p<0.001). With E/e'

Table 3. Receiver operating characteristic analysis

Control vs. Patient	AUC	p value	Cut-off	Sensitivity	Specificity	PPV+	PPV-
NT-proBNP	0.787	<0.001	95.55	53.66	100.00	100.0	57.8
E/e'	0.844	<0.001	9	86.36	73.08	84.4	76.0

*Values for area under the curve may be interpreted for NT-proBNP and E/e' (p<0.05).

Table 4. Correlation between NT-type natriuretic peptide, E/e', and characteristics of patients with predialysis chronic renal failure

		NT-proBNP	E/e'
Age (years)	r	0.456	0.361
	p	0.003	0.016
GFR	r	-0.383	-0.345
	p	0.013	0.022
Albumin	r	-0.492	-0.346
	p	0.001	0.021
PTH	r	0.445	0.159
	p	0.004	0.304
Phosphorus	r	0.190	0.378
	p	0.233	0.012
Proteinuria	r	0.177	0.301
	p	0.267	0.047

*Spearman Correlation Analysis; r, correlation coefficient.

cutoff value of 15, the sensitivity was 86.36% and specificity was identified as 73.08%. This result supports the idea of diastolic dysfunction among CKD patients.

In addition to left ventricle echocardiographic measurements, atrial measurements provide information about cardiac function. The reason for providing information about increased volume load and diastolic dysfunction in the early period is that left atrium diameter and volume have prognostic significance in kidney failure patients. Left atrium measurements also provide information about acute variations in extracellular volume.[13] In our study, the mean values for left atrium diameter were higher in the patient group compared to the control group. These data support information that volume load and diastolic dysfunction are observed more in CKD patients.

BNP is basically found in the ventricular myocardium with myocardial wall tension the actual stimulant for secretion.[14] An increase in natriuretic peptides is known from several studies in recent years with CKD patients. This increase is due to extracellular and ventricular volume increase. The increase in natriuretics is simultaneously known to be linked to reduced renal clearance. The correlation between NT-proBNP and eGFR stated that reduction in the renal elimination of NT-proBNP limited the use of this plasma biomarker in CKD patients.[15] However, when a recent cohort study is examined, NT-proBNP was shown to be a potent predictor of cardiovascular outcomes in predialysis CKD patients, in spite of potential contradictions.[16] A study evaluating heart failure in CKD patients examined the correlation with natriuretic peptides and identified a poor correlation with BNP. However, NT-proBNP level, an inactive metabolite formed by the destruction of BNP in serum, was shown to have a stronger correlation in renal failure patients.[17] When we examine our study results, we identified a significantly high degree of NT-proBNP levels in those with predialysis chronic renal disease. Another study by Anwaruddin et al.[18] researching the association between dyspnea in chronic renal failure patients stated that NT-proBNP was diagnostic for heart failure in CKD patients attending the emergency service with dyspnea. A multicentric randomized study in Canada investigated 500 patients attending seven different emergency services with dyspnea complaints. The mean NT-proBNP level was identified as 3697 pg/mL in 230 cases with heart failure diagnosed, whereas it was 212 pg/mL in those without heart failure ($p<0.00001$) and that knowing NT-proBNP results would reduce emergency service visit durations by 21% and the number of patients readmitted to the hospital within 60 days by 35%.[19] These findings point to the importance of NT-proBNP in the diagnosis and management of heart failure, common in CKD patients frequently with hypervolemia beforehand and beginning as diastolic dysfunction, while still asymptomatic.

In our study, when we examine the correlation between NT-proBNP results and echocardiographic parameters. It was identified that NT-proBNP and E/e' were each a significant parameter for disease. In many studies[5,11] 15 was used as E/e' cutoff value, though Kim et al.[20] used 11 and we identified 9 as the cutoff (Fig. 2, sensitivity 86.36%, specificity 73.08%). In general, values of <300 pg/mL exclude heart failure; however, as is known that the cutoff for all stages of CKD is still undefined for CKD patients. We concluded the cutoff for NT-proBNP of 95.55 and above was associated with the presence of disease (Fig. 1, sensitivity 53.66%, specificity 100%). NT-proBNP is a beneficial cardiac marker for prognosis and cardiovascular risk classification in the CKD population and echocardiography can be used to play a significant and complementary duty in cardiovascular risk profile assessment.

There are some restrictions to our study. First, it was performed in a single center. Second, our study included patients treated at the clinic and there are relatively low patient numbers. In addition, there were patients using antihypertensive medications in the patient group and the effects on results cannot be excluded. This type of study may be expanded by increasing the patient numbers. By taking the essential precautions and treatments with awareness of heart failure, whereas still asymptomatic among CKD patients, especially the patients' quality of life and future treatments may be reduced.

CONCLUSION

In our study, NT-proBNP and E/e' were identified to be important parameters for the prediction of diastolic dysfunction in chronic renal failure patients without clinical findings of heart disease. There is a need for larger prospective studies to research this topic and clarify the place and usefulness of both NT-proBNP and E/e' ratio in clinical practice.

Ethics Committee Approval

This study approved by the Taksim Training and Research Hospital Clinical Research Ethics Committee (Date: 12.12.2018, Decision No: 111).

Informed Consent

Prospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: B.B.; Design: B.B., S.Ö.; Supervision: O.M.; Fundings: S.Ö.; Materials: S.Ö., Ü.B.; Data: S.Ö., O.Z.; Literature search: B.B., S.Ö.; Writing: S.Ö., B.B.; Critical revision: K.K.

Conflict of Interest

None declared.

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Diyaliz Öncesi Kronik Böbrek Yetmezliği Hastalarında Hacim Yükünün Belirlenmesi İçin Diyastolik Disfonksiyon ve Nt-ProBNP Ölçümünün Önemi

Amaç: KBH hastalarında hacim fazlalığı sıklıkla gözlenir ve zamanla diyastolik disfonksiyona ve bunun devamında kalp yetmezliğine neden olabilir. Bu çalışmada, sol ventrikül dolum basıncı ile ilişkili ve son zamanlarda kullanıma giren E/e' oranı ile kalp yetmezliğinde önemli bir belirteç olan NT-proBNP arasındaki ilişkiyi belirlemeyi amaçladık.

Gereç ve Yöntem: Çalışmaya normal sol ventrikül ejeksiyon fraksiyonu olan ve kardiyovasküler hastalığı olmayan (25 kadın, 19 erkek) 44 övolemik KBH hastası ve 26 sağlıklı gönüllü (15 kadın, 11 erkek) dahil edildi. Plazma NT-proBNP seviyeleri ELISA yöntemiyle ölçüldü ve tüm katılımcılar, NT-proBNP seviyeleri ile tepe erken diyastolik mitral hız ile tepe erken diyastolik mitral anüler hız oranı arasındaki ilişkiyi araştırmak için transtorasik konvansiyonel doppler ve doku doppler ekokardiyografi ile değerlendirildi (E/e').

Bulgular: Hasta grubu 25 kadın (%56.8) ve 19 erkek (%43.2) olup, yaş ortalaması 59.36±9.26 yıl idi. Sağlıklı gönüllüler, yaş ortalaması 58.58±10.39 yıl olan 15 kadın (%57.7) ve 11 erkek (%4.23) oluşturmuştur. Hasta grubunda NT-proBNP düzeyleri ve E/e' değerleri kontrol grubuna göre daha yüksek bulundu (p<0.001). NT-proBNP için 300 pg/mL cut-off değeri baz alındığında duyarlılık %53.66 ve özgüllük %100 olarak bulundu. E/e' cut-off değeri 15 ile duyarlılık %86.36 ve özgüllük %73.08 olarak belirlendi.

Sonuç: Çalışmamızda NT-proBNP ve E/e' değerlerinin klinik kalp yetmezliği bulgusu olmayan kronik böbrek yetmezliği hastalarında diyastolik disfonksiyonu öngörmede önemli parametreler olduğu belirlendi. Hem NT-proBNP'nin hem de E/e' oranının klinik pratikteki yerini ve kullanışlılığını doğrulamak için bu konuyu araştıran daha geniş, kapsamlı ve ileriye dönük çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Diyastolik disfonksiyon; E/e'; kronik böbrek yetmezliği; NT-proBNP.