ORIGINAL ARTICLE

NT-proBNP level in stage 3-4 chronic kidney disease and mortality in long-term follow-up: HAPPY study subgroup analysis

Evre 3 ve 4 kronik böbrek yetersizliğinde NT-proBNP düzeyi ve uzun dönem takipte mortalite: HAPPY çalışması alt grup analizi

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ABSTRACT

Objective: This was an investigation of the relationship between the N-terminal pro-brain natriuretic peptide (NT-proBNP) level and mortality in patients with stage 3-4 chronic kidney disease (CKD).

Methods: This study was designed as a subgroup analysis of the Heart Failure Prevalence and Predictors in Turkey (HAPPY) study. The HAPPY study included 4650 randomly selected individuals from the 7 geographical regions of Turkey. A total of 191 subjects from the original cohort with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.1.73 m² were enrolled in this study and the relationship between NT-proBNP and mortality was investigated. Prognostic variables for total and cardiovascular mortality were also examined using Cox regression analysis.

Results: The mean length of follow-up was 76.12±22.45 months. The mean NT-proBNP level was 423.54±955.88 pg/mL. During follow-up, 51 subjects (26.7%) died from any cause and 36 subjects (18.8%) died from a cardiovascular cause. The presence of hypertension (hazard ratio [HR]: 1.89; 95% confidence interval [CI]: 1.01–3.50; p=0.048), anemia (HR: 2.49; 95% CI: 1.20–5.15; p=0.014), male gender (HR: 2.64; 95% CI: 1.44–4.86; p=0.002) and log NT-proBNP (HR: 4.93; 95% CI: 2.83-8.58; p<0.001) were independent variables for total mortality. The presence of hypertension (HR: 2.47; 95% CI: 1.09–5.56; p=0.029), male gender (HR: 2.79; 95% CI: 1.38–5.62; p=0.004), eGFR (HR: 0.94; 95% CI: 0.91–0.98; p=0.005) and log NT-proBNP (HR: 6.31; 95% CI: 3.11–12.81; p<0.001) were independent predictors of cardiovascular mortality.

Conclusion: NT-proBNP was found to be an independent prognostic marker in patients with stage 3–4 CKD.

ÖZET

Amaç: Bu çalışmada, evre 3-4 kronik böbrek hastalığı (KBH) olanlarda N-terminal pro-beyin natriüretik peptid (NT-proBNP) düzeyleri ile mortalite arasındaki ilişkiyi araştırmayı amaçladık.

Yöntemler: Çalışma "Türkiye'deki kalp yetersizliği prevalansı ve öngördürücüleri (HAPPY)" çalışmasının alt grup analizi olarak planlandı. HAPPY çalışmasında Türkiye'nin 7 coğrafi bölgesinden rastgele seçilen 35 yaş üstü 4650 hasta alındı. Bu çalışmaya ise tahmini glomerüler filtrasyon hızı (eGFR) 60 ml dk -1/1.73 m² altında olan 191 hasta dahil edildi. NT-proBNP ile mortalite arasındaki ilişki araştırıldı. Ayrıca Cox regresyon analizi kullanılarak toplam ve kardiyovasküler mortalite için prognostik değişkenler saptandı.

Bulgular: Ortalama takip süresi 76.12±22.45 aydı. Ortalama NT-proBNP düzeyi 423.54± 955.88 pg/mL idi. Takipte 51 katılımcı (%26.7) herhangi bir nedene bağlı ve 36 katılımcı (%18.8) kardiyovasküler nedene bağlı hayatını kaybetti. Hipertansiyon [Tehlike oranı (HR): 1.89; %95 güven aralığı (GA) 1.01–3.50; p=0.048], anemi (HR: 2.49; %95 GA 1.20–5,15; p=0.014), erkek cinsiyet (HR: 2.64 %95 GA 1.44–4,86; p=0.002 ve log NT-proBNP düzeyi (HR: 4.93; %95 GA 2.83–8.58; p<0.001) toplam mortalite için bağımsız öngördürücülerdi. Hipertansiyon (HR: 2.47; %95 GA 1.09–5.56; p=0.029), erkek cinsiyet (HR: 2.79; %95 GA 1.38–5,62; p=0.004, eGFR (HR: 0.94; %95 GA 0.91–0.98; p=0.005) ve log NT-proBNP düzeyi (HR: 6.31; %95 GA 3.11–12.81; p<0.001) ise kardiyovasküler mortalite için bağımsız öngördürücülerdi.

Sonuç: Bu çalışmada evre 3–4 KBH hastalarında NT-proBNP'nin güçlü bağımsız bir prognostik belirteç olduğu gösterilmiştir.

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Chronic kidney disease (CKD) is a serious global health problem.[1] The worldwide prevalence of stage 3–5 CKD is 10.6%.[2] The estimated prevalence is even higher in low or middle income countries, reaching up to 14.3%, with a profound impact on healthcare economics.[3] Cardiovascular causes are one of the most common etiological factors of mortality in CKD patients[4] and the risk increases with a declining estimated glomerular filtration rate (eGFR).[5]

N-terminal pro-brain natriuretic peptide (NT-proBNP) is a biomarker widely used in the diagnosis and management of cardiovascular disease, and it also has significant prognostic implications.[6] The serum level of NT-proBNP rises in response to several physiological and biochemical factors,[7] and an elevated level of NT-proBNP is an expected finding in patients with CKD due to reduced renal clearance. Therefore, determining the prognostic relationship between NT-proBNP and cardiovascular disease in patients with CKD remains challenging.

The aim of this study was to investigate the relationship between NT-proBNP and mortality in patients with CKD.

METHODS

Study population, data acquisition, and definition of end points

A flow chart of the study is shown in Figure 1. Participants were selected from the previously published Heart Failure Prevalence and Predictors in Turkey (HAPPY) trial population. The HAPPY trial investigated the prevalence of heart failure in Turkey using NT-proBNP measurement in a population of 4650 subjects selected from the 7 geographical regions of the country. Any heart disease, abnormal electrocardiogram findings, or an NT-proBNP level ≥120 pg/mL was considered an indication to perform echocardiography. An NT-proBNP level >2000 pg/mL was diagnosed as heart failure without further imaging analysis. In the overall cohort, 20% had an NT-proBNP level ≥120 pg/mL. The prevalence of heart failure was 2.9%. A detailed description of the rationale, methodology, and results of the HAPPY trial has been previously reported.[8]

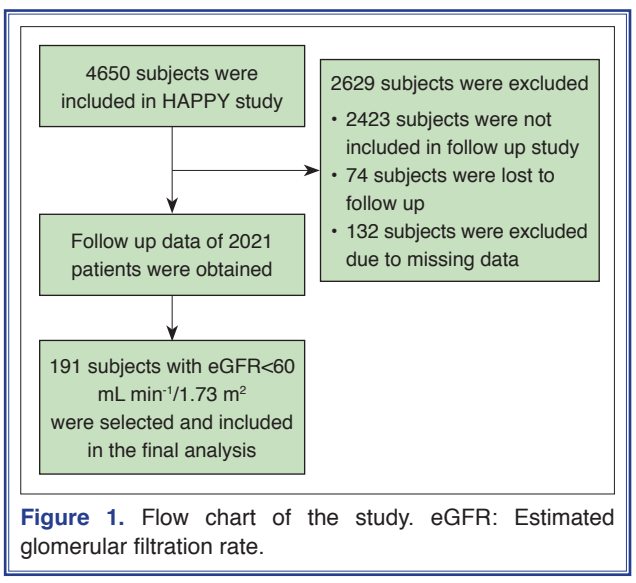

Figure 1. Flow chart of the study. eGFR: Estimated glomerular filtration rate.

Abbreviations:

ACR	*Albumin to creatinine ratio*
AUC	*Area under the curve*
CI	*Confidence interval*
CKD	*Chronic kidney disease*
DKD	*Diabetic kidney disease*
GN	*Glomerulonephritis*
eGFR	*Estimated glomerular filtration rate*
ESRD	*End-stage renal disease*
HAPPY	*Heart Failure Prevalence and Predictors in Turkey*
HR	*Hazard risk*
NT-proBNP	*N-terminal pro-brain natriuretic peptide*
PKD/TIN	*Polycystic kidney disease/ tubulointerstitial nephritis*
ROC	*Receiver operating characteristic*

For the current study, subjects with an eGFR <60 mL/min-1/1.73 m^2 were selected from the 2021 participants of HAPPY study whose long-term total and cardiovascular mortality data could be obtained.[9] The eGFR level at least 1 month before enrollment was also reviewed to exclude any possible acute kidney injury. The demographic data, cardiovascular risk factors, and laboratory parameters were obtained from the original HAPPY trial data. The eGFR was calculated using the Cockroft-Gault formula. In addition to the original study parameters, a spot urinary albumin to creatinine ratio (ACR) was calculated for each patient. Total mortality was defined as mortality from any cause, including cardiovascular mortality. Cardiovascular mortality was defined as mortality from cardiovascular causes, including myocardial infarction, arrhythmia, heart failure, and stroke. Mortality data were obtained and verified from medical records and death certificates.

Statistical analysis

Continuous variables were expressed as mean±SD or median (interquartile range) and compared using analysis of variance or the Kruskal-Wallis test. The association between 2 continuous variables was ana-

lyzed using the Pearson correlation method. Categorical variables were compared using a chi-square test. Logarithmic transformation was used in the statistical analyses due to the high skewness of the NT-proBNP levels. The cut-off value of NT-proBNP for total or cardiovascular mortality was assessed using receiver operating characteristic (ROC) analysis. The cumulative survival of participants with a NT-proBNP level above or below this cut-off value was compared using Kaplan-Meier analysis. To identify independent predictors of all-cause death and cardiovascular death, a multivariable Cox proportional hazards model was constructed. Parameters from the univariate analysis with a p value <0.25 at baseline were used in the multivariable model as covariates. Multicollinearity between the univariate predictors was avoided using a correlation coefficient of 0.7. The model for total mortality included age, gender, the presence of hypertension, the presence of anemia, an ACR >30 mg/g, and the log NT-proBNP. The model for cardiovascular mortality included the presence of hypertension, the presence of anemia, gender, a history of coronary artery disease, an ACR >30 mg/g, the eGFR, and the log NT-proBNP.

Compliance with ethical standards

Informed consent was obtained from all of the participants included in the study. All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The datasets generated during and/or analyzed during the current study are not publicly available due to national regulatory action, but are available from the corresponding author on reasonable request.

RESULTS

The baseline demographic and clinical data of the participants are summarized in Table 1. Only 13 subjects (6.8%) had an ACR >30 mg/g. The majority of patients had stage 3 CKD (184 subjects, 96.3%). There was no stage 5 patient in the study group. The patients who died during follow-up were significantly older, male gender, and the presence of anemia was significantly higher in this group. The mean NT-proBNP level was 423.54± 955.88 pg/mL and the mean eGFR was 49.21±8.94 mL/min^{-1}/1.73 m^2 (Table 2).

The mean length of follow-up was 76.12±22.45 months. During follow-up, 51 subjects (26.7%) died from any cause and 36 subjects (18.8%) died from a cardiovascular cause. The NT-proBNP level was significantly higher and the eGFR level was significantly lower in subjects who died from any cause or a cardiovascular cause compared with subjects who survived. The laboratory parameters according to the mortality status are presented in Table 2.

There was a weak, but significant, negative correlation between the eGFR and log NT-proBNP (r=-0.267; p<0.001). A weak, but significant, positive cor-

Table 1. Baseline demographic and clinical data of the study population

	Overall (n=191)	Survival (n=140)	Mortality (n=51)	*p* value
Age (years) (mean±SD)	66.29±12.67	64.01±12.98	72.56±9.36	<0.001
Male gender, n (%)	79 (41.4)	48 (25.1)	31 (16.2)	0.001
Diabetes mellitus, n (%)	37 (19.4)	26 (13.6)	11(5.8)	0.64
Hypertension, n (%)	109 (57.1)	78 (40.8)	31 (16.2)	0.62
Previous coronary heart disease, n (%)	14 (7.3)	7 (3.7)	7 (3.7)	0.57
Dyslipidemia, n (%)	126 (66.0)	88 (46.1)	38 (19.9)	0.13
Anemia, n (%)	20 (10.5)	6 (3.2)	14 (7.3)	<0.001
ACR >30 mg/g, n (%)	13 (6.8)	9 (4.7)	4 (2.1)	0.73
Chronic kidney disease, n (%)				
Stage 3a	142 (74.3)	113 (59.2)	29 (15.2)	0.001
Stage 3b	42 (22.0)	25 (13.1)	17 (8.9)	
Stage 4	7 (3.7)	2 (1.0)	5 (2.6)	

ACR: Urinary albumin to creatinine ratio; SD: Standard deviation.

Table 2. Baseline laboratory parameters of the study population

	Overall (n=191)	Survival (n=140)	Mortality (n=51)	*p* value
	Mean±SD	Mean±SD	Mean±SD	
Serum creatinine (mg/dL)	1.35±0.59	1.33±0.55	1.42±0.68	0.36
Serum uric acid (mg/dL)	5.14±1.55	4.91±1.44	5.78±1.68	0.002
eGFR (mL/min/1.73 m²)	49.21±8.96	50.74±7.65	45.01±10.85	<0.001
Hemoglobin (g/dL)	13.12±1.33	13.20±1.22	12.90±1.58	0.169
Total cholesterol (mg/dL)	207.50±42.89	231.06±43.80	192.22±36.50	0.002
High-density lipoprotein (mg/dL)	43.80±12.08	44.86±11.95	40.87±12.07	0.043
ACR (mg/g)	10.01±35.62	23.14±1.95	56.94±7.97	0.059
NT-proBNP (pg/mL)	423.54±955.88	191.88±303.13	1059.46±1629.07	<0.001

ACR: Urinary albumin to creatinine ratio; eGFR: Estimated glomerular filtration rate; NT-proBNP: N-terminal pro-brain natriuretic peptide; SD: Standard deviation.

Table 3. Cox proportional hazard analysis for total mortality

	B	Exp (B)	95.0% CI for Exp (B)		*p* value
			Lower	Upper	
Age	0.030	1.031	1.002	1.060	0.037
Male gender	0.974	2.649	1.442	4.866	0.002
Anemia	0.914	2.494	1.206	5.154	0.014
Hypertension	0.637	1.890	1.005	3.555	0.048
Urinary albumin to creatinine ratio >30 mg/g	-0.277	0.941	0.252	2.285	0.623
Log N-terminal pro-brain natriuretic peptide	1.597	4.937	2.837	8.589	<0.001

CI: Confidence interval.

Table 4. Cox proportional hazard analysis for cardiovascular mortality

	B	Exp (B)	95.0% CI for Exp (B)		*p* value
			Lower	Upper	
Previous coronary heart disease	0.296	1.345	0.491	3.682	0.564
Male gender	1.028	2.796	1.389	5.627	0.004
Anemia	0.577	1.780	0.712	4.449	0.217
Hypertension	0.905	2.471	1.097	5.567	0.029
Urinary albumin to creatinine ratio >30 mg/g	-0.796	0.451	0.127	1.605	0.219
Log N-terminal pro-brain natriuretic peptide	1.843	6.317	3.114	12.817	<0.001
Estimated glomerular filtration rate	-0.055	0.947	0.911	0.984	0.005

CI: Confidence interval.

relation between the ACR and log NT-proBNP was also observed (r=0.228; p=0.002).

Cox proportional hazard analysis was performed to obtain independent variables affecting total and cardiovascular mortality. The presence of hypertension (hazard ratio [HR]: 1.89; 95% confidence interval [CI]: 1.01–3.50; p=0.048), anemia (HR: 2.49; 95% CI: 1.20–5.15; p=0.014), male gender (HR:

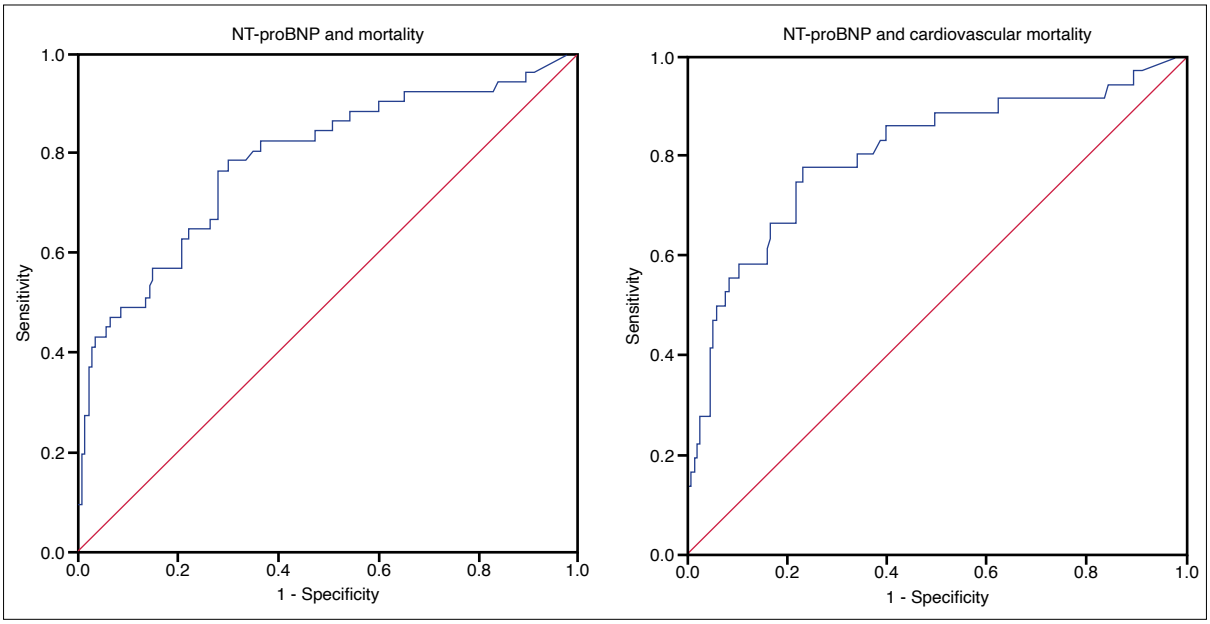

Figure 2. Receiver operating characteristic curve analysis of N-terminal pro-brain natriuretic peptide (NT-proBNP) and mortality.

2.64; 95% CI: 1.44–4.86; p=0.002), and log NT-proBNP (HR: 4.93; 95% CI: 2.83–8.58; p<0.001) were independent variables for total mortality (Table 3), and the presence of hypertension (HR: 2.47; 95% CI: 1.09–5.56; p=0.029), male gender (HR: 2.79; 95% CI: 1.38–5.62; p=0.004), eGFR (HR: 0.94; 95% CI: 0.91–0.98; p=0.005) and log NT-proBNP (HR: 6.31; 95% CI: 3.11–12.81; p<0.001) were independent predictors of cardiovascular mortality (Table 4).

ROC analysis revealed 197 pg/mL as the log NT-proBNP cut-off value for total mortality (sensitivity 76%, specificity 72%; area under the curve [AUC]: 0.785; p<0.001) and 251 pg/mL for cardiovascular mortality (sensitivity 78%, specificity 77%; AUC: 0.840; p<0.001) (Fig. 2).

Kaplan-Meier analysis revealed a significantly decreased survival of participants with an NT-proBNP level above the cut-off value (p<0.001 for both total and cardiovascular mortality) (Fig. 3).

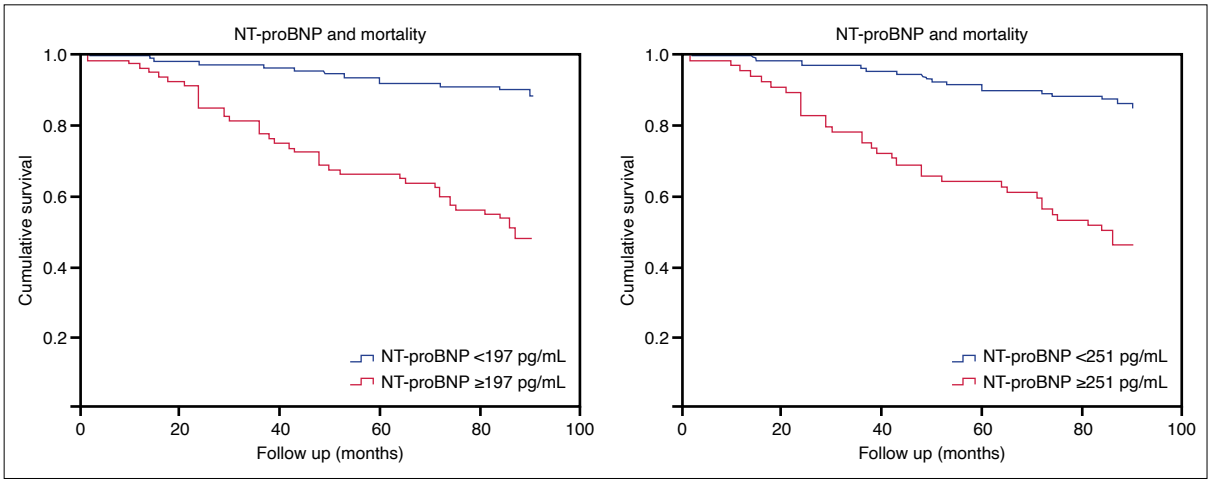

Figure 3. Kaplan-Meier analysis for **(A)** total mortality and **(B)** and cardiovascular mortality according to N-terminal pro-brain natriuretic peptide (NT-proBNP) cut-off values.

DISCUSSION

The NT-proBNP level is higher in patients with CKD than the patients with preserved renal function due to the decreased renal clearance[10] and possible volume overload. In our study population, the mean NT-proBNP was 423.54±955.88 pg/mL (min-max: 5–8377 pg/mL). Previous studies have indicated that the increase in NT-proBNP level has prognostic implications.[11,12] Consistent with other research, we found that 1 SD unit increase in log NT-proBNP significantly increased the risk of total mortality by 4.9 times and cardiovascular mortality by 6.3 times. The presence of anemia or hypertension as well as male gender also increased the risk of mortality but not as much as NT-proBNP. Although establishing a cut-off value for NT-proBNP as a prognostic marker is challenging, to our knowledge, we report for the first time that NT-proBNP cut-off levels of 195 pg/mL and 251 pg/mL predict all-cause and cardiovascular death, respectively, with moderate specificity and sensitivity.

The role of NT-proBNP as a prognostic marker in CKD has been investigated in several studies. Gregg et al.[13] analyzed the effect of CKD on the relationship between circulating or imaging cardiac markers with all-cause death or cardiovascular death or events. They followed 3218 patients with a preserved eGFR with albuminuria for a mean duration of 12.5 years and found that NT-proBNP significantly predicted mortality in patients without previous coronary artery disease (adjusted HR: 3.20; 95% CI: 1.83–5.60). The adjusted HR of NT-proBNP in our study is higher. This may be explained by the different study populations, and it is also possible that the prognostic predictive power of NT-proBNP may increase in stage 3–5 CKD patients compared with stage 1–2. Additional randomized control studies are needed to justify this hypothesis.

Though our study lacks data about the etiology of CKD in the study group, etiological factors in these patients may influence the effect of NT-proBNP on mortality. Langsford et al.[14] prospectively examined 1157 patients with an eGFR 15–45 mL/min^{-1}/1.73 m^2. They compared prognostic factors between 3 etiological groups: diabetic kidney disease (DKD), glomerulonephritis (GN) and polycystic kidney disease/tubulointerstitial nephritis (PKD/TIN). Among patients with DKD, an increase in NT-proBNP per SD was associated with 68% increased mortality, which was not seen in patients with GN or PKD/TIN. This finding may suggest that the prognostic effect of NT-proBNP in CKD depends on the etiology of the disease. It is reasonable to postulate that the common vascular mechanisms underlying diabetic kidney disease and elevated NT-proBNP may explain the increased mortality in this population.

Landray et al.[15] investigated the relevance of baseline characteristics to the risk of end-stage renal disease (ESRD) and death in 382 patients from the Chronic Renal Impairment in Birmingham study cohort. Similar to our study results, they found that age, NT-proBNP level, cigarette smoking, and troponin T level were independent factors affecting all cause death, and the NT-proBNP level and age were the strongest predictors of these 4 factors.

During the course of CKD, several comorbid situations occur that contribute to mortality. One is anemia, which results from disturbed iron handling due to chronic disease status, a shortened life span of erythrocytes, and most importantly, decreased erythrocyte production from bone marrow due to erythropoietin insufficiency.[16] In our study, anemia was an independent predictor of mortality. There are similar findings in previous studies. Sato et al.[17] investigated 62,931 patients and grouped them into 6 categories according to eGFR and hemoglobin levels. In the group with an eGFR below 45 mL/min^{-1}/1.73 m^2, anemia independently increased the risk of death 3.3 times.

The prognostic role of cardiac biomarkers such as NT-proBNP seems to be more important than renal markers in patients with CKD. Matshushita et al. enrolled 8622 patients from the Atherosclerosis Risk in Communities Study and investigated the predictive role of 5 nontraditional cardiac and kidney markers on the risk of a cardiovascular event. They found that the strength of the risk prediction model, including conventional risk factors, significantly increased with the addition of troponin T and NT-proBNP. However, only cystatin C improved the model among renal markers. Urinary ACR was not found to be an independent risk factor for mortality in our study, contrary to previous research. This may be due to the presence of a relatively low number of subjects with an ACR >30 mg/g.

Limitations

Our study has several limitations. First of all, the study population was not randomly selected, so this

fact should be taken into account while interpreting the results. Second, the etiological factors of CKD could not be obtained, which might affect the role of NT-proBNP as a predictor of mortality. Third, no stage 5 or ESRD patient was included, and the majority of the patients were in the stage 3 CKD group, which may limit the generalization of the results to the entire group of stage 3-5 patients. Fourth, only a baseline NT-proBNP level was available, and the amount and effect of change in NT-proBNP throughout the follow-up period could not be determined. Fifth, the use of diuretics as well as volume status of the subjects could not be determined, which may have affected the NT-proBNP values.

Conclusion

In patients with an eGFR <60 mL/min^{-1}/1.73 m^2, NT-proBNP significantly and independently predicted all-cause and cardiovascular mortality in long-term follow-up. Future studies are needed to establish the mechanism underlying this finding as well as to incorporate NT-proBNP in prognostic risk models for CKD patients.

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