Original Paper

NT-proBNP in the Prognosis of Death or Need for Renal Replacement Therapy in Patients with Stage 3–5 Chronic Kidney Disease

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Keywords

N-terminal prohormone of brain natriuretic peptide · Chronic kidney disease · Prognosis · Survival

Abstract

Background: The risk of cardiovascular (CV) complications is much greater in patients with chronic kidney disease (CKD). The aim of this study was to assess predictors of mortality, renal failure progression, and the need for dialysis in patients with CKD. **Methods:** The study group consisted of 70 patients with stage 3–5 CKD, followed up on average for 33.4 ± 15.6 months. Laboratory tests and echocardiography were performed on all patients. Composite endpoints were defined as (1) all-cause mortality and (2) mortality or renal replacement therapy (RRT), defined as the initiation of dialysis therapy. **Results:** During the observation period, 13 patients died and 11 began dialysis therapy. NT-proBNP was found to be a significant predictor in receiver operating characteristic curve analysis for all study endpoints. The optimal cutoff value for NT-proBNP as a predictor of mortality was 569.8 pg/mL, with a sensitivity of 53.8% and a specificity of 89.1%. For mortality or RRT, the cutoff value for NT-proBNP was 384.9 pg/mL, with a sensitivity and specificity of 70.8 and 72.7%, respectively. In a multivariate regression analysis, NT-proBNP was an independent predictor of mortality with an OR = 7.5 (95% CI: 1.05–53.87; $p = 0.044$) and of mortality or RRT with an OR = 4.7 (95% CI: 1.01–22.66; $p = 0.048$). **Conclusions:** NT-proBNP is an independent predictor of mortality in patients with CKD and can also be useful for CV risk stratification in this patient population.

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Introduction

The risk of cardiovascular (CV) complications is much greater in patients with chronic kidney disease (CKD) than in the general population [1]. The increased mortality risk in this patient population is specifically due to rapidly developing CV complications during the progression of this serious metabolic disorder. This risk increases 2- to 3-fold already in CKD stage 2 according to the National Kidney Foundation – Kidney Disease Outcomes Quality Initiative (NKF KDOQI) classification [2], and even 10- to 100-fold when a patient begins dialysis [3]. Following kidney transplantation, this risk significantly decreases; however, it still remains 5-fold higher than in the general population [4]. Apart from classic CV risk factors, in the course of CKD, additional – i.e., nonclassic risk factors – appear, such as oxidative stress, chronic inflammation, endothelial dysfunction, accelerated atherosclerosis, and increased arterial stiffness [1, 5, 6]. Moreover, such patients often present with hyperhydration or anemia as well as disorders of lipid and calcium-phosphate regulation, which significantly worsen the already complicated metabolic condition.

The entire spectrum of CV diseases comprising ischemic heart disease (IHD) may develop in patients with CKD. However, frequently, asymptomatic and silent myocardial ischemia dominates clinically in this CKD population [7, 8]. Additionally, secondary to CKD, left ventricular (LV) diastolic dysfunction may develop, leading to congestive heart failure (CHF) with a preserved LV ejection fraction, which predominates in this population of patients [9–11]. Moreover, heart arrhythmias, due to dyselectrolytemia, volumic disorders, and LV hypertrophy, are common in this group of patients, significantly increasing the risk of CV death.

Recently, much attention has been devoted worldwide to natriuretic peptides and their prognostic value for patients with IHD, especially following myocardial infarction, as well as for patients with CHF and pulmonary embolism [12–15]. The most frequently assayed natriuretic peptide in clinical practice is N-terminal prohormone of brain natriuretic peptide (NT-proBNP), secreted in cardiomyocytes under the conditions of pressure and volume overload in cardiac chambers [16]. It has been proved that in CKD patients, elevated NT-proBNP levels are, on the one hand, associated with the advancement of kidney disease and may, on the other hand, also serve as a prognostic parameter [17], although the latter option is much less well documented. In our study, we assessed the influence of laboratory parameters, with particular attention given to NT-proBNP, and of echocardiographic parameters on the survival of non-dialysis patients with stage 3–5 CKD in long-term observation.

The aim of the study was to assess predictors of mortality, renal failure (RF) progression, and the onset of dialysis therapy in a population of patients with CKD.

Patients and Methods

The study group consisted of 70 patients (31 male and 39 female) with stage 3–5 CKD aged 67.7 ± 12.2 years followed up at our Nephrology Outpatient Clinic. The following laboratory values were tested in all patients: creatinine, estimated glomerular filtration rate (eGFR) calculated with the modified MDRD formula, phosphate, calcium, urea, parathormone, and serum NT-proBNP.

All patients also underwent echocardiography, conducted with a GE Vivid S6 device equipped with a 2.5-MHz transducer with electrocardiographic lead recording. In the parasternal long-axis view, the following parameters were assessed: LV end-diastolic dimension, right ventricular end-diastolic dimension, left atrial dimension, interventricular septal diameter, LV posterior wall dimension, and LV fractional shortening [18]. The LV mass (LVM) was calculated with the Devereux formula and the LVM index by indexing LVM by the body surface area of the patient [19].

In a 4-chamber view, the LV ejection fraction was calculated with the simplified Simpson rule. Using the M-Mode in a 4-chamber view, tricuspid and mitral annular plane systolic excursion were assessed. By placing the Doppler gate at the tips of the mitral valve leaflets, the mitral flow profile was assessed, as well as early (E) and late (A) transmitral velocities and the deceleration time of the early transmitral flow velocity. The E/A ratio was also calculated. On tissue Doppler echocardiography, the velocities' profile was obtained. By placing the Doppler gate on the lateral mitral annulus at the posterior leaflet of the mitral valve, peak mitral annular systolic velocity and peak mitral early diastolic velocity were measured. Similarly, by placing the Doppler gate on the septal mitral annulus at the anterior leaflet, peak septal mitral early diastolic velocity was assessed. In order to estimate the LV filling pressure, the average early diastolic velocity was calculated based on septal and lateral mitral velocities, and the ratio of early mitral flow to the average early diastolic mitral velocity was calculated [18].

All Doppler parameters were recorded as the patients lay in the left lateral position and breathed normally, and they were assessed as the mean of measurements taken in 3 consecutive cardiac cycles. Renal replacement therapy (RRT) was defined as the initiation of dialysis therapy during the observation period.

The patients' details and mortality data were collected during control visits in the Nephrology Outpatient Clinic, from hospital records, and from the National Health Fund. In our study, the composite endpoints consisted of (1) all-cause mortality and (2) mortality or the onset of dialysis therapy. The study protocol was approved by the Bioethics Committee (No. 555/2011) and all patients consented in writing to their inclusion in the research.

Statistical Analysis

Values of parameters with a normal distribution are presented as mean $\pm$ standard deviation, whereas values with nonnormal distributions are expressed as median and range. In order to compare groups, Student's *t* test and the Mann-Whitney test were employed depending on the parameters' distribution, and the χ^2 test was used to compare qualitative values in contingency tables. To evaluate the prognostic significance of the assessed parameters, univariate and multivariate regression analysis was employed. Based on the receiver operating characteristic (ROC) curve analysis, values which best characterized the patients were selected.

In order to graphically present patient survival in relation to the NT-proBNP levels obtained in the ROC analysis, Kaplan-Meier curves and log-rank testing were used; log transformation was used to normalize the distribution of serum NT-proBNP levels.

Results

The study group consisted of 70 patients (31 male and 39 female) with stage 3–5 CKD aged 67.7 ± 12.2 years followed up on average for 33.4 ± 15.6 months. Among these 70 patients, 20 patients were in the 4th CKD stage, 9 patients in the 5th CKD stage, and the remaining 41 patients in the 3rd CKD stage. During this period, 13 patients died and 11 began dialysis therapy; 70% of the patients underwent rehospitalization. The clinical, echocardiographic, and biochemical characteristics of the CKD patients, comparing the survivors with the nonsurvivors, are presented in Table 1. The patients from the nonsurvivor group, as compared to the survivor group, were significantly older and had significantly higher levels of NT-proBNP and phosphate, while the differences in tricuspid annular plane systolic excursion, mitral flow E/A ratio, and level of urea had a tendency towards statistical significance. Interestingly, no significant differences in creatinine levels and eGFR were observed between the two groups.

ROC Analysis

The area under the ROC curve for NT-proBNP as a predictor of mortality in the study population amounted to 0.714 (95% CI: 0.591–0.817). The calculated value for NT-proBNP of 569.8 pg/mL based on this analysis was characterized by a sensitivity of 53.8% and a specificity of 89.1% for the occurrence of death (Fig. 1a).

Fig. 1. Receiver operating characteristic curve analysis for NT-proBNP to predict mortality (a) and mortality or renal replacement therapy (b).

Fig. 2. Kaplan-Meier analysis for NT-proBNP as a predictor of mortality.

The area under the ROC curve for NT-proBNP as a predictor of the endpoint defined as mortality or RRT was 0.755 (95% CI: 0.635–0.851). The optimal cutoff value in the ROC curve analysis for NT-proBNP was 384.9 pg/mL. For this cutoff, the sensitivity and specificity of endpoint occurrence was 70.8 and 72.7%, respectively (Fig. 1b).

The significant prognostic parameters from ROC curve analysis are presented in Table 2.

Univariate and Multivariate Regression Analysis

To evaluate the prognostic significance of the endpoints mortality and mortality or RRT, the OR was estimated for each demographic, laboratory, and echocardiographic parameter. The analysis accounted for the parameters' variability. Additionally, an analysis of the parameters as dichotomous variables was conducted, based on the values calculated by ROC curve analysis.

Table 1. Clinical, echocardiographic, and biochemical characteristics of CKD patients comparing survivors with nonsurvivors

Variable	All patients (n = 70)	Survivors (n = 57)	Nonsurvivors (n = 13)	p
Age, years	67.7±12.2	65.7	76.3	0.003
Male, n (%)	31 (44)	27 (47)	4 (31)	0.276
Arterial hypertension, n (%)	59 (84)	48 (84)	11 (85)	0.971
Diabetes, n (%)	17 (24)	13 (23)	4 (31)	0.545
CAD, n (%)	5 (7)	3 (5)	2 (15)	0.201
Smokers, n (%)	20 (29)	15 (26)	5 (38)	0.381
Rehospitalization, n (%)	49 (70)	41 (72)	8 (62)	0.460
BMI	27.9 (21.3–44.1)	29.2 (21.3–44.1)	27.7 (24.8–41.3)	0.717
Creatinine, mg/dL	1.65 (1.02–6.31)	1.57 (1.02–6.3)	2.17 (1.02–5.9)	0.280
eGFR, mL/min	32.4±14.3	33.7±13.6	26.8±16.4	0.114
Urea, mg/dL	64 (20–204)	61 (20–204)	98 (39–163)	0.087
Phosphate, mg/dL	3.99±1.04	3.87±1.03	4.56±0.95	0.034
Calcium, mg/dL	9.10±0.85	9.08±0.87	9.17±0.75	0.747
Hemoglobin, g/dL	12.5±1.71	12.6±1.6	12.1±2.0	0.344
Parathormone, pg/mL	83.1 (27.7–407.9)	81 (27–407)	95 (30–274)	0.932
NT-proBNP, pg/mL	293.3 (32.6–12,633)	239 (33–2,931)	643 (58–12,633)	0.017
LVDD, cm	4.7±0.5	4.7±0.5	4.5±0.3	0.272
RVDD, cm	2.7±0.2	2.7±0.2	2.8±0.2	0.178
LAD, cm	4.1±0.5	4.1±0.5	4.1±0.5	0.787
LVMI	97.7 (57.9–198.0)	97 (58–198)	107 (69–127)	0.487
IVSd, cm	1.1 (0.9–1.5)	1.1 (0.9–1.5)	1.1 (1.0–1.4)	0.511
LVPWd, cm	1.1 (0.9–1.5)	1.1 (0.9–1.5)	1.1 (1.0–1.3)	0.815
LVEF, %	59.1±5.2	59.4±5.5	58.0±3.4	0.393
FS, %	30.5±3.5	30.7±3.7	29.9±2.1	0.492
TAPSE, mm	24±3	25±3	23±2	0.073
MAPSE, mm	13 (11–17)	13 (11–17)	13 (11–16)	0.799
E, cm/s	6.2 (3.5–12)	6.2 (3.5–12.0)	5.7 (3.8–10.0)	0.341
A, cm/s	8.2 (4.7–14.6)	8.2 (4.7–14.1)	8.4 (6.4–14.6)	0.468
DT, ms	233±58	229±52	249±81	0.263
E/A ratio	0.73 (0.42–1.9)	0.75 (0.42–1.90)	0.65 (0.46–1.14)	0.083
Em Avg	7.0±2.0	7.1±2.0	6.2±2.0	0.127
E/Em Avg ratio	9.3 (5.1–24.8)	9.2 (5.1–24.8)	9.5 (5.6–17.1)	0.491
SmLV, cm/s	7.0 (5.0–14.0)	7.0 (5.0–14.0)	7.0 (6.0–11.0)	0.545

Values are presented as mean ± SD or median (range) unless specified otherwise. CKD, chronic kidney disease; CAD, coronary artery disease; BMI, body mass index; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; LVDD, left ventricular end-diastolic dimension; RVDD, right ventricular end-diastolic dimension; LAD, left atrial dimension; LVMI, left ventricular mass index; IVSd, interventricular septal diameter; LVPWd, left ventricular posterior wall dimension; LVEF, left ventricular ejection fraction; FS, fractional shortening; TAPSE, tricuspid annular peak systole excursion; MAPSE, mitral annular peak systole excursion; E, early transmittal peak velocity; A, late transmittal peak velocity; DT, deceleration time; Em Avg, average peak mitral early diastolic velocity; SmLV, peak mitral annular systolic velocity.

The results of the univariate and multivariate regression analyses for the assessed variables as predictors of mortality in the study group are presented in Table 3. Independent predictors of mortality were age with an OR of 1.1 (95% CI: 1.01–1.19; $p = 0.022$) and NT-proBNP with an OR of 7.5 (95% CI: 1.06–53.87; $p = 0.043$).

In the multivariate regression analysis, NT-proBNP was found to be the only significant predictor of mortality or RRT (Table 4).

Table 2. Significant prognostic parameters from ROC analysis

Parameter	Mortality		Mortality or onset of dialysis	
	AUC	95% CI	AUC	95% CI
Age	0.769	0.653–0.861	0.593	0.469–0.709
NT-proBNP	0.713	0.591–0.817	0.755	0.635–0.851
Phosphate	0.695	0.572–0.801	0.725	0.603–0.826

ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

Table 3. Predictors of mortality among CKD patients from univariate and multivariate analysis

Variable	Univariate <i>p</i> value	Multivariate <i>p</i> value	OR	Lower 95% CI	Upper 95% CI
Age	0.0017	0.02	1.1	1.01	1.19
Rehospitalization	0.008	ns	NA	NA	NA
NT-proBNP >569.8 pg/mL	0.006	0.044	7.5	1.05	53.87
Urea (mg/dL)	0.035	ns	NA	NA	NA

CKD, chronic kidney disease; CI, confidence interval; NT-proBNP, N-terminal pro B-type natriuretic peptide.

Table 4. Predictors of mortality or renal replacement therapy in CKD patients from univariate and multivariate analysis

Variable	Univariate <i>p</i> value	Multivariate <i>p</i> value	OR	Lower 95% CI	Upper 95% CI
Rehospitalization	0.0001	ns	NA	NA	NA
Hemoglobin (mg/mL)	0.05	ns	NA	NA	NA
NT-proBNP >384.9 pg/mL	0.0003	0.048	4.7	1.01	22.66
Urea (mg/dL)	0.001	ns	NA	NA	NA
Creatinine (mg/dL)	0.0001	ns	NA	NA	NA
log PTH	0.0003	ns	NA	NA	NA

CKD, chronic kidney disease; CI, confidence interval; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; log PTH, logarithm of parathormone.

Survival Analysis according to NT-proBNP Levels

During the 4-year follow-up, 13 patients (19%) died. In the nonsurvivor group, the level of NT-proBNP was statistically significantly higher than in the survivor group ($p = 0.017$). Figure 2 presents the result of the Kaplan-Meier survival analysis depending on whether the level of NT-proBNP was above or below the value of 569.8 pg/mL as obtained by ROC curve analysis. The patients with levels of NT-proBNP above 569.8 pg/mL were characterized by a significantly worse survival prognosis than the patients with NT-proBNP levels below or equal to 569.8 pg/mL ($p = 0.00036$).

Discussion

In our study, we demonstrated that in CKD patients, NT-proBNP was an independent predictor of either of the prespecified endpoints: (1) mortality and (2) mortality or RRT. As indicated in the Introduction, mortality rates in the course of CKD are highest when patients receive dialysis [1, 20]. The published literature and our results indicate that such high mortality rates are also associated with significantly high levels of NT-proBNP [17].

Our results are consistent with other reports which proved that NT-proBNP is an independent predictor of death for patients receiving dialysis [21–23]. Voroneanu et al. [24] demonstrated that among 98 patients treated with dialysis followed up for 24 months, NT-proBNP >14,275 pg/mL was the only independent predictor of death with an HR of 1.83 ($p = 0.023$). The sensitivity and specificity of this value of NT-proBNP as a predictor of death as obtained by ROC curve analysis was 68.7 and 79.3%, respectively, and the surface area under the ROC curve was 0.722. In another study, NT-proBNP was also an independent predictor of mortality among patients who received peritoneal dialysis [25]. Of all renal replacement therapies, peritoneal dialysis is characterized by the highest risk of hyperhydration; thus, NT-proBNP seems to have a particularly significant prognostic value in this group of patients [26].

In our study, NT-proBNP was an independent predictor of mortality also in combination with RRT, which was defined as onset of dialysis therapy. The majority of reports concerning this subject discuss advanced stages of CKD (stages 3–5) with eGFR >60 mL/min/1.73 m² and/or patients who receive dialysis. This is mostly because in this phase of CKD, metabolic disorders exacerbate and the activity of all atherogenic factors increases, leading to an increased CV risk, including sudden cardiac death [27]. After the initiation of dialysis therapy, the situation is considerably worsened by side effects of RRT, i.e., fluctuations in systemic pressure, dyselectrolytemia, absence of biocompatible dialysis liquids, and hemorrhagic and/or thrombotic disorders. Consequently, the majority of researchers focus their attention on the population of dialysis patients.

The number of reports focusing on this issue and analyzing non-dialysis patients with CKD is very limited. Consequently, it needs to be stressed that in our study, NT-proBNP proved to be an independent predictor of mortality also in the non-dialysis period.

In our study, the NT-proBNP value obtained by ROC curve analysis was much smaller than those found in the abovementioned studies conducted among patients receiving dialysis, and amounted to 569.8 pg/mL with a sensitivity of 53.8% and a specificity of 89.1% for predicting death and a surface area under the ROC curve of 0.714. Similarly, in their work, Vickery et al. [28] demonstrated that for non-dialysis patients with CKD, an NT-proBNP level ≥ 89 pmol/L was an independent predictor of death with an HR of 2.5 ($p < 0.05$). Lower NT-proBNP values which indicate a higher risk of mortality among non-dialysis CKD patients are directly related to less advanced RF and a specific activity mechanism of this substance and its transformations and effects, partly dependent on the level of decrease in GFR [29].

The natural process of NT-proBNP synthesis and secretion in stretched cardiomyocytes increases hyperhydration. This provokes a balancing mechanism in the form of natriuresis and diuresis. NT-proBNP is also a hormonally active oligopeptide. It inhibits the activity of the renin-angiotensin-aldosterone system, the synthesis of renin and aldosterone, and sympathetic stimulation. All these mechanisms result in vasodilation [30]. In CKD, as glomerular filtration decreases due to the progressive loss of nephrons, this process loses its effector function, which – combined with hyperhydration – leads to NT-proBNP oversynthesis. In their study, Vickery et al. [29] demonstrated that each decrease in GFR of 10 mL/min was associated with a 38% increase in the level of NT-proBNP. Consequently, in CKD, due to a partial dependence of the level of this substance on RF advancement, hyperhydration, and/

or dialysis, relatively higher NT-proBNP values are observed than in the general population. However, these values are not as high as during dialysis [29]. It is not surprising, then, that the NT-proBNP levels associated with a high CV risk among the patients receiving dialysis in the aforementioned reports are several times higher than in a population of non-dialysis CKD patients. This is evidently associated with decreased diuresis and the permanent, often severe, and resistant hyperhydration in this patient population.

Natriuretic peptides are also a valuable tool for the detection of systolic and diastolic LV dysfunction [31]. Despite the dependence of their levels on the already described decrease in eGFR and volemic variations, these peptides may become an effective measure of LV remodeling and function in CKD. This is particularly significant because CHF is detected in approximately 60% of patients with CKD and is an important underlying cause of CV complications [32]. It has been proven that levels of natriuretic peptides in patients with a similar LV dysfunction are significantly higher when RF is a coexisting condition and correlate positively with a decrease in GFR. Another study has demonstrated that both BNP and NT-proBNP are significant indicators of LV hypertrophy and IHD in asymptomatic patients with CKD with no need for dialysis [33]. In 2008, Bruch et al. [34] presented their results on 341 patients with CHF (the observation period was 620 ± 353 days), of whom 54% also had renal dysfunction. They demonstrated that NT-proBNP was an independent predictor of sudden cardiac events among CHF patients with coexisting CKD and those without coexisting CKD.

The interpretation of NT-proBNP levels in patients with CKD and coexisting CHF may prove to be difficult because cutoff values for NT-proBNP are unknown for this patient population. In our study, for the two endpoints, i.e., mortality and mortality or onset of dialysis therapy, two different cutoff points for NT-proBNP were obtained, and each was an independent predictor of these occurrences. In some patients participating in our study, we detected echocardiographic features of LV diastolic dysfunction with lowered early mitral diastolic velocities. This was the group of patients with features of LV diastolic dysfunction not yet presenting with overt CHF, which can be qualified as a risk group for its development.

What is very interesting with our results is that NT-proBNP not only was an independent predictor CKD patient mortality, but also had a predictive value for CKD exacerbation and the onset of dialysis.

Consequently, this allows us to intensify nephro- and cardioprotective activities, i.e., prescribing restrictive diets; avoiding infections and their appropriate treatment; and strict control of arterial pressure, volemia, and metabolic disorders. All these activities are known to slow disease progression and therefore to delay the initiation of RRT [35].

The abovementioned research results show a significant clinical value in assaying NT-proBNP levels in patients with different CKD stages. However, the lack of measurement standardization and different cutoff points in the conducted studies for different clinical conditions do not permit clinicians to base unequivocal therapeutic decisions on these measurements alone. We believe, however, that among patients with CKD, especially without overt CHF symptoms, elevated NT-proBNP levels may detect those patients who are beginning to develop symptoms of LV diastolic dysfunction even before the appearance of overt CHF with all its symptoms. Most importantly, such increased NT-proBNP levels allow for the identification of those CKD patients whose RF may be rapidly progressing. The recognition of NT-proBNP as a potential risk factor for progression and worse prognosis in CKD while at the same time being a predictor of CV complications, which constitute the main reason for the increased mortality rates in this patient population, is – in our opinion – an important contribution towards the constant search for universal predictive factors in this high-risk patient population.

Study Limitations

The major limitation of our study is the relatively small size of the study group, which is from only one research center. Another potential drawback is the assessment of all-cause mortality without the identification of CV deaths. However, due to the small total number of deaths ($n = 13$), any subdivision into further groups would have definitely made statistical analyses more difficult.

Conclusions

We believe that NT-proBNP may serve as an adjuvant predictor, useful for risk stratification among CKD patients. Thus, it may enrich the heterogeneous CV risk scale in CKD, which is not standardized in many nephrology centers and mostly based only on clinical data, yet still so important when qualifying patients for kidney transplantation. The indisputable value of NT-proBNP, however, resulting from our study and evident in worldwide reports, is the role of this parameter as an independent risk factor for death both in the general population and among patients with CKD at every stage.

Statement of Ethics

The authors of this manuscript declare that they complied with the Principles of Ethical Publishing presented in the Declaration of Helsinki and that the study protocol was approved by a local ethics committee (IRB approval No. 555/2011). Informed consent was obtained from all participants included in the study.

Disclosure Statement

The authors declare that no conflict of interest exists.

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