ORIGINAL ARTICLE

N-terminal pro-B-type natriuretic peptide as a marker of hypervolemia and predictor of increased mortality in patients on hemodialysis

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KEY WORDS

cardiovascular complications, hemodialysis, N-terminal pro-B-type natriuretic peptide, overhydration, prognosis

ABSTRACT

INTRODUCTION N-terminal pro-B-type natriuretic peptide (NT-proBNP) is an established biomarker of heart failure in the general population. However, its diagnostic value is unclear in hemodialysis (HD) patients owing to renal insufficiency.

OBJECTIVES The aim of the study was to establish the usefulness of NT-proBNP for hydration assessment and the relation of NT-proBNP to the nutritional state and prognosis of survival.

PATIENTS AND METHODS In 321 HD patients (206 men; mean age, 65.1 ±21.4 years), we assessed NT-proBNP levels, overhydration (OH_{BIA}), and the indices of the nutritional state (using a bioimpedance analysis [BIA]) in relation to cardiac troponin T (cTnT), hemoglobin, albumin, total cholesterol (TC), and C-reactive protein (CRP) levels. The efficacy of HD was assessed using Kt/V, weekly HD dose, and HD session ultrafiltration. The cohort was divided into NT-proBNP quartiles. Patients with 2 NT-proBNP measurements were categorized also into change-over-time subgroups. A follow-up lasted for a median period of 23.8 ±26.3 months.

RESULTS Relative OH_{BIA} increased across the NT-proBNP quartiles (Q1/Q2/Q3/Q4, 1.31% ±2.56%/2.06% ±2.35%/2.92% ±2.97%/4.62% ±4.22%; P <0.0001). NT-proBNP was also closely associated with other OH parameters. In addition, there was a significant correlation between NT-proBNP and cTnT (r = 0.55; P <0.0001). Body mass index (BMI) and fat tissue index (FTI) decreased across the quartiles (BMI, 28.5 ±7.7/26.0 ±6.6/25.8 ±5.4/23.7 ±5.5 kg/m^2; FTI, 14.4 ±9.0/14.1 ±7.3/12.3 ±6.8/11.6 ±6.1; P <0.001). The highest albumin level was present in Q1 (4.10 ±0.63/3.99 ±0.51/3.90 ±0.62/3.97 ±0.78 g/dl; P = 0.006). The TC level was the lowest in Q4 (190 ±60/169 ±56/173 ±51/153 ±56 mg/dl; P = 0.002). The hemoglobin level decreased across the quartiles (11.44 ±1.25/11.15 ±2.50/10.79 ±1.51/10.45 ±1.67 g/dl; P = 0.0006). The differences in CRP levels and HD-related parameters were nonsignificant. During the follow-up, 97 deaths were recorded (11/26/21/39, P <0.0001).

CONCLUSIONS NT-proBNP seems to be a useful biomarker of hypervolemia in HD patients. Nevertheless, it has to be interpreted with regard to the patient's individual residual renal function and cardiovascular status.

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INTRODUCTION Chronic kidney disease (CKD), with end-stage renal disease (ESRD) as its final phase, has emerged as one of the most challenging healthcare issues in developed countries. Each year about 440 000 individuals are introduced to renal replacement therapy (RRT) worldwide.[1] Among patients treated with hemodialysis (HD), the most common modality of RRT, the annual mortality rate varies from 5% to 27%, depending on the country.[2] Cardiovascular (CV) risk in this group is significantly higher compared with their sex- and age-matched healthy counterparts, and CV disease, the leading cause of death, accounts for nearly 50% of all deaths.[3,4] In younger patients

(under 45 years old) undergoing dialysis, the CV risk can be up to 100-fold greater compared with the general population, and this trend is evident also in young dialyzed women.[5] The list of causes for CV mortality includes, among others, sudden cardiac death, pulmonary thromboembolism, myocardial infarction, arrhythmias, and stroke.[1] Apart from traditional CV risk factors, ESRD patients are burdened with uremia-related factors such as overhydration, chronic low-grade inflammation, malnutrition, anemia, hyperphosphatemia, and vitamin D deficiency.[6,7] As a result, CKD patients suffer from several disorders restricted mainly to this condition, including severe mineral and bone disorders linked to vascular calcification, as well as electrolyte and water imbalance, accelerated aging, and many others.[1] The spectrum of CKD-related disorders is so extensive that a special multifactorial diagnostic and therapeutic approach is necessary, which also includes the need for developing appropriate, sensitive, reproducible, and affordable prognostic markers. The family of natriuretic peptides, owing to their association with the hydration status, seems to be particularly promising.

Brain natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are well-established gold standard biomarkers of heart failure (HF) in the general population. They are synthetized by the myocytes of the heart ventricles as a result of the BNP gene expression in response to volume- or pressure-dependent myocardial stretch. The immature 108-aminoacid proBNP, which is a secondary product of the gene transcription, is cleaved in a one-to-one ratio into 2 compounds: biologically active 32-aminoacid BNP and 76-aminoacid NT-proBNP, an inert N-terminal remainder of the synthesis.[8,9] After the release into the circulation, BNP binds to membrane-linked receptors located in the liver, lung, kidney, and vascular endothelium, exerting its physiological functions, namely, diuresis, natriuresis, and vasodilation.[10,11] In short, natriuretic peptides protect against volume overload and its long-term effects such as heart remodeling, and are natural opponents to the renin–angiotensin–aldosterone system.[3] BNP is removed from the circulation using enzymatic processes, receptor-mediated mechanisms (natriuretic peptide receptor type C), and only partially through renal clearance, whereas NT-proBNP is eliminated mostly by the kidneys. This explains why these 2 peptides have different half-lives (21 minutes for BNP and 60 to 120 minutes for NT-proBNP) and why, in CKD, BNP levels may be less dependent on renal function.[9,11-14] Among healthy individuals, the circulating levels of BNP and NT-proBNP are higher in women than in men and increase with age.[8] Their levels may be elevated also in CV diseases other than HF, such as valvular and congenital heart disorders, arrhythmias, myocarditis, acute coronary syndrome, stroke, and also in some non-CV disorders such as bacterial sepsis, acute respiratory distress syndrome, severe anemia, and burns.[8] Due to the fact that the kinetics of natriuretic peptides are altered by renal dysfunction, the interpretation of circulating natriuretic peptide levels in relation to HF in HD patients may be difficult.[10]

The assessment of the hydration status of patients undergoing dialysis is particularly important. The ability to accurately measure the amount of excess fluid volume, overhydration (OH), is an area of particular interest for nephrologists because this is needed to achieve adequate volume control in patients undergoing HD and to reduce the risk for CV complications.[7] Traditional methods of OH evaluation include the observation of interdialytic weight gain, blood pressure, presence of edema, measurement of the cardiothoracic index or inferior vena cava diameter—some of them being very subjective or highly impractical and difficult to implement in the clinical setting.[15] Therefore, the introduction of the bioimpedance analysis (BIA) has been an important improvement. The BIA enables a noninvasive, inexpensive, objective assessment of hydration status in clinical practice.[16] Proper volume management and avoidance of OH are thought to reduce hypertension, related heart remodeling, risk for CV complications, and death rates.[17]

The main goal of our study was to assess the usefulness of NT-proBNP as a marker of hypervolemia, with a BIA as a comparative method in our cohort of HD patients. We also aimed to establish the value of NT-proBNP as a prognostic marker and searched for a relationship between NT-proBNP and patients' inflammatory and nutritional status.

PATIENTS AND METHODS

Study design

This prospective multicenter observational study was performed in a cohort of 321 patients (206 men; 115 women; mean age, 65.1 ±21.4 years) suffering from ESRD who were treated with maintenance HD. Patients were recruited from 3 different HD centers (132, 107, and 82 patients, respectively). Patients with a history of implantable cardioverter defibrillator, joint endoprosthesis surgery, and amputations were excluded owing to contraindications to a BIA. Otherwise there were no exclusion criteria related to comorbidities, and all patients willing to participate were enrolled. The study protocol was approved by a local ethics committee. Prior to obtaining written consent, patients were provided with a detailed study description and were informed of the risks and benefits of participation in the study. A study design defined 2 observation points (OP) for each subject—the first one during the screening and inclusion process (OP1) and the second one during the follow-up (OP2). OP2 was performed in 67.6% (n = 217) of the initial patients after a median time of 35.0 ±1.3 weeks. The remaining patients were lost to follow-up for several reasons including death, renal transplant, transfer to peritoneal dialysis or to another HD center. At each OP, a medical history was taken, physical examination

performed, body composition assessed, and blood samples collected.

Body composition parameters were estimated using the BIA (Body Composition Monitor, Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany), yielding indices of OH including absolute ($absOH_{BIA}$) and relative ($relOH_{BIA}$; $absOH_{BIA}$, l/actual body weight, kg expressed in %), total body water (TBW), extra- and intracellular water (ECW, ICW), ECW/TBW ratio as well as body mass index (BMI), fatty tissue index (FTI), and lean tissue index (LTI). The measurements were performed shortly before mid-week HD session in a supine position using 4 disposable electrodes attached in pairs to the patient's hand and foot contralateral to the arteriovenous fistula, as per the device manual.

Blood samples were collected before the mid-week HD session. Laboratory tests were aimed at multifactorial evaluation of the studied patients. CV condition was assessed using serum NT-proBNP (pg/ml, Elecsys® assay, Roche Diagnostics, Basel, Switzerland) and cardiac troponin T levels (cTnT, Elecsys® Troponin T fourth generation assay, Roche Diagnostics, Basel, Switzerland). We also used serum albumin, hemoglobin, and total cholesterol (TC) concentrations to assess the nutritional status as well as C-reactive protein (CRP) to assess the inflammatory state. We decided to estimate residual renal function with patient-reported daily diuresis (PRDD), whereas HD efficacy was assessed with Kt/V (Daugirdas), HD session ultrafiltration (HDuf) and weekly HD dose understood as the number of hours of dialysis per week (HDdose).

For statistical purposes, the study group was divided into quartiles according to NT-proBNP levels (Q1–3, n = 80 each, and Q4, n = 81). Patients with 2 NT-proBNP estimation points (n = 217) were also categorized according to changes in NT-proBNP concentrations into 4 subgroups: "decrease" ($\Delta\log_{10}$ NT-proBNP < lower quartile, n = 55), "increase" ($\Delta\log_{10}$ NT-proBNP > upper quartile, n = 55), and the remaining into "stable high" (OP1 $\log_{10}$ NT-proBNP > median, n = 54), and "stable low" (OP1 $\log_{10}$ NT-proBNP ≤ median, n = 53). The entire cohort was observed for a median time of 23.8 ±26.3 months to record mortality.

Statistical analysis A statistical analysis was performed using STATISTICA 10 (StatSoft Inc., Tulsa, Oklahoma, United States). NT-proBNP values were log-transformed before further calculations and analysis. Interval variables were tested for normality using the Shapiro–Wilk test. We employed either the analysis of variance with the NIR post-hoc test or the Kruskal–Wallis test with the Dunn's post-hoc test for a comparison between quartiles. Differences in nominal variables were assessed with the χ^2 test. All correlations were performed using the Spearman correlation coefficient. The differences for paired variables (comparison between OPs) were analyzed using either the Wilcoxon matched-pair test or the *t* test for paired variables, depending on normality. A survival analysis was concluded using Kaplan–Meier curves with the χ^2 test to test significance. Finally, a Cox proportional hazard regression model was built to determine potential prognostic predictors. A *P* value of less than 0.05 was considered significant. Variables with normal distribution were expressed as mean ± standard deviation, whereas variables with nonnormal distribution—as a median value ± interquartile range.

RESULTS **Cohort characteristics** Diabetic kidney disease was the leading cause of ESRD in the studied cohort (18.7%, n = 60), followed by glomerulonephritis (17.1%, n = 55), ischemic nephropathy (10.6%, n = 34), polycystic kidney disease (8.4%, n = 27), and several others. In 36 patients (11.2%), the cause of ESRD was not established. There were no significant differences between the NT-proBNP quartiles with regard to subjects' age, sex distribution, incidence rates of diabetes mellitus, past history of myocardial infarction, stroke, or length of follow-up. Throughout the follow-up, 97 patients died (30.2% of the entire cohort), 24 received kidney graft (7.5%), while 4 were lost to follow-up due to transfer to peritoneal dialysis or other HD centers, and 1 was discontinued from RRT. The remaining 195 patients were alive and remained in the study. Selected parameters and cohort characteristics recorded during OP1 are presented in TABLE 1.

Hydration, cardiovascular, and hemodialysis parameters OH according to the BIA, both absolute ($absOH_{BIA}$) and relative ($relOH_{BIA}$), increased across the higher quartiles of NT-proBNP with the highest values in Q4 (P <0.0001). The same trend was present for the ECW/TBW ratio with the highest values observed in Q4 and Q2 (P = 0.0003). However, the post-hoc analysis showed that the differences in the ECW/TBW ratio were significant only for Q1 vs Q2 and Q1 vs Q4 (P = 0.03 and P = 0.0001, respectively). At the same time, there were significant strong correlations between $\log_{10}$ NT-proBNP and the above parameters ($absOH_{BIA}$, r = 0.41, P <0.0001; $relOH_{BIA}$, r = 0.44, P <0.0001; and ECW/TBW ratio, r = 0.24, P <0.0001). All correlations are presented in TABLE 2. On the contrary, PRDD was adequately decreasing across the quartiles (P <0.0001) with a negative correlation with $\log_{10}$ NT-proBNP (r = -0.32; P <0.0001). Furthermore, we found a strong correlation between increased values of NT-proBNP and cTnT reflected both as a correlation (r = 0.55; P <0.0001) and as a steady cTnT increase across the studied quartiles (P <0.0001). Similar correlations with cTnT were present for both OH_{BIA} parameters (r = 0.39; P <0.0001). Variations and correlations in terms of the recorded blood pressures, Kt/V, HDdose, and HDuf were nonsignificant. Statistical comparisons between OPs for the studied quartiles did not reveal any relevant differences (data not shown); therefore, we decided to

TABLE 1 Characteristics of patients on maintenance hemodialysis

Variable	All patients (n = 321)	NT-proBNP levels				*P* value
		quartile 1 (n = 80)	quartile 2 (n = 80)	quartile 3 (n = 80)	quartile 4 (n = 81)	
age, y	65.2 ±21.4	64.9 ±22.4	65.6 ±21.1	64.9 ±20.5	63.3 ±22.6	NS (0.33)
men, %	64.2	72.5	63.8	57.5	63.0	NS (0.25)
fatal outcome	30.2	13.8	32.5	26.3	48.2	<0.0001
CV, %	16.5	6.3	21.3	12.5	25.9	NS (0.57)
non-CV, %	13.7	7.5	11.3	13.8	22.2	
diabetes, %	32.7	27.5	37.5	36.3	29.6	NS (0.35)
HD vintage, wk	178.7 ±200.0	154.1 ±136.6	176.9 ±158.3	170.6 ±234.3	237.0 ±245.6	0.03
$absOH_{BIA}$, l	1.90 ±2.20	1.10 ±2.10	1.60 ±1.80	2.20 ±2.15	2.90 ±3.30	<0.0001
$relOH_{BIA}$, %	2.55 ±3.41	1.31 ±2.56	2.06 ±2.35	2.92 ±2.97	4.62 ±4.22	<0.0001
ECW/TBW ratio	0.503 ±0.052	0.491 ±0.049	0.508 ±0.059	0.501 ±0.049	0.515 ±0.060	0.0003
BMI, kg/m^2	25.9 ±6.5	28.5 ±7.7	26.0 ±6.6	25.8 ±5.4	23.7 ±5.5	<0.0001
FTI, kg/m^2	13.2 ±7.1	14.4 ±9.0	14.1 ±7.3	12.3 ±6.8	11.6 ±6.1	0.0002
LTI, kg/m^2	11.5 ±3.5	12.4 ±3.4	11.2 ±2.8	11.6 ±3.5	11.3 ±3.2	0.01
NT-proBNP, pg/ml	6098 ±19 659	985 ±933	3571 ±2238	10 142 ±8003	35 000 ±2863	<0.0001
cTnT, ng/ml	0.049 ±0.058	0.026 ±0.033	0.042 ±0.037	0.061 ±0.046	0.094 ±0.122	<0.0001
albumin, g/dl	4.00 ±0.65	4.10 ±0.63	3.99 ±0.51	3.90 ±0.62	3.97 ±0.78	0.006
hemoglobin, g/dl[a]	10.95 ±1.53	11.44 ±1.25	11.15 ±2.50	10.79 ±1.51	10.45 ±1.67	0.0006
TC, mg/dl	171 ±62	190 ±60	169 ±56	173 ±51	153 ±56	0.002
CRP, mg/l	7.31 ±11.00	6.65 ±11.02	7.50 ±9.37	7.29 ±10.50	7.92 ±20.26	NS (0.38)
PRDD, ml	1000 ±1350	1000 ±1500	875 ±1250	550 ±1450	400 ±1000	<0.0001
HDuf, ml	2300 ±1900	2000 ±2700	2550 ±1400	2200 ±2000	2300 ±2050	NS (0.69)
HDdose, h	12.0 ±0.5	12.0 ±0.5	12.0 ±0.5	12.0 ±0.5	12.0 ±0.5	NS (0.81)
SBP, mmHg[a]	138.1 ±20.3	137.5 ±17.9	136.7 ±22.6	139.2 ±19.5	139.0 ±21.3	NS (0.86)
DBP, mmHg[a]	80.0 ±20.0	80.0 ±15.0	80.0 ±20.0	80.0 ±20.0	80.0 ±15.0	NS (0.65)
MBP, mmHg[a]	101.0 ±13.8	100.7 ±12.3	99.7 ±14.7	102.1 ±13.2	101.4 ±12.7	NS (0.71)

a values expressed as mean ± standard deviation; the remaining values are presented as median ± interquartile range or percentage.

Abbreviations: $absOH_{BIA}$, absolute overhydration according to bioimpedance analysis; BMI, body mass index; CRP, C-reactive protein; cTnT, cardiac troponin T; CV, cardiovascular; DBP, diastolic blood pressure; ECW/TBW, extracellular water to total body water; FTI, fat tissue index; HD, hemodialysis; HD vintage, preceding time on HD; HDdose, number of hours of dialysis per week; HDuf, HD session ultrafiltration; LTI, lean tissue index; MBP, mean blood pressure; NS, nonsignificant; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PRDD, patient-reported daily diuresis; $relOH_{BIA}$, relative overhydration according to bioimpedance analysis; SBP, systolic blood pressure; TC, total cholesterol

analyze these parameters in the subgroups according to changes in NT-proBNP correlations (TABLE 3). A decrease in NT-proBNP levels was associated with a reduction in both OH parameters ($absOH_{BIA}$, $P = 0.0003$, and $relOH_{BIA}$, $P = 0.0004$) as well as a significant reduction in cTnT levels ($P = 0.003$). Opposite effects were observed in the "increase" group. A decline in PRDD was also noted in the "increase" group (750 ±1400 ml vs 350 ±1000 ml, $P = 0.001$). Changes in Kt/V, HDdose, HDuf, and blood pressures were nonsignificant.

Nutritional, inflammatory, and other parameters

The highest median albumin level was present in Q1 and the lowest—in Q3; however, the post-hoc analysis revealed that the differences for albumin were significant only for Q1. TC levels were the lowest in Q4, followed by Q2; however, again, the differences were significant only between Q1 and Q4 ($P = 0.0008$). On the contrary, hemoglobin levels decreased steadily across the quartiles ($P = 0.0006$; TABLE 1). These trends were supported by inverse correlations between log_{10} NT-proBNP levels and the above parameters (TABLE 2). BMI and FTI decreased almost similarly in consecutive quartiles ($P < 0.0001$ and $P = 0.0002$, respectively). Surprisingly, LTI was the lowest in Q2 and peaked in Q1 ($P = 0.01$ in the post-hoc analysis). The

TABLE 2 Spearman correlation coefficients between N-terminal pro-B-type natriuretic peptide and other parameters in patients on maintenance hemodialysis (n = 321)

	Parameter	*r*	*P* value		Parameter	*r*	*P* value
hydration, CV, and HD	cTnT	0.55	<0.0001	nutrition	BMI	−0.29	<0.0001
	$relOH_{BIA}$	0.45	<0.0001		FTI	−0.23	<0.0001
	$absOH_{BIA}$	0.41	<0.0001		LTI	−0.11	NS (0.06)
	PRDD	−0.32	<0.0001		hemoglobin	−0.26	<0.0001
	ECW/TBW	0.24	<0.0001		TC	−0.25	0.0001
	MBP	0.06	NS (0.33)		albumin	−0.20	0.0007
	Kt/V	0.07	NS (0.36)	inflammation	CRP	0.12	NS (0.09)
	HDdose	−0.05	NS (0.46)	other	HD vintage	0.16	0.0053
	HDuf	0.01	NS (0.87)		age	−0.01	NS (0.88)

Abbreviations: see TABLE 1

TABLE 3 Differences in the most important parameters between the two observation points in the subgroups according to changes in N-terminal pro-B-type natriuretic peptide levels in patients on maintenance hemodialysis

		Stable low (n = 53)	Decrease (n = 55)	Increase (n = 55)	Stable high (n = 54)
NT-proBNP, pg/ml	OP1	2013 ±2606	13519 ±30253	2700 ±5712	27198 ±19140
	OP2	2199 ±2572	2960 ±4424	18014 ±28762	35000 ±16147
	P value	NS (0.21)	<0.0001	<0.0001	0.03
cTnT, ng/ml	OP1	0.043 ±0.036	0.047 ±0.052	0.043 ±0.059	0.106 ±0.137
	OP2	0.037 ±0.03	0.040 ±0.039	0.060 ±0.066	0.101 ±0.098
	P value	NS (0.39)	0.003	0.0006	NS (0.31)
$absOH_{BIA}$, l	OP1	1.55 ±1.50	2.20 ±2.10	1.50 ±1.80	2.60 ±2.50
	OP2	1.10 ±1.55	1.00 ±1.90	2.30 ±2.90	2.85 ±2.90
	P value	NS (0.65)	0.0003	0.01	NS (0.72)
$relOH_{BIA}$, %	OP1	1.75 ±1.98	2.82 ±3.00	2.02 ±2.48	4.54 ±3.65
	OP2	1.37 ±2.29	1.45 ±2.63	3.44 ±3.55	4.43 ±4.24
	P value	NS (0.61)	0.0004	0.008	NS (0.65)
hemoglobin, g/dl	OP1	11.40 ±1.80	10.90 ±1.90	11.30 ±1.90	11.00 ±2.00
	OP2	11.15 ±1.10	11.40 ±1.60	10.70 ±2.10	10.80 ±1.60
	P value	0.02	NS (0.11)	0.003	NS (0.45)
all-cause mortality (*P* = 0.027)		11 (20.7)	8 (14.5)	19 (34.5)	19 (35.2)

Data are expressed as median ± interquartile range or number (percentage) of patients.

Abbreviations: OP1, first observation point; OP2, second observation point; others, see TABLE 1

tendencies for BMI and FTI were confirmed by significant correlations (both $P < 0.0001$), whereas the relationship between $\log_{10}$ NT-proBNP and LTI was nonsignificant ($P = 0.06$). No significant differences in inflammatory markers between the NT-proBNP quartiles or correlations for CRP were observed. In addition, we found an association between $\log_{10}$ NT-proBNP and HD vintage ($r = 0.16$; $P = 0.005$) with the differences between the quartiles ($P = 0.03$). A comparison between the OPs revealed a decrease in hemoglobin levels in patients from the "increase" group ($P = 0.003$; TABLE 3). Moreover, "stable high" subjects showed a reduction in LTI and BMI (11.1 ±3.5 vs 10.5 ±3.3, $P = 0.005$; 23.5 ±4.9 vs 23.3 ±4.9, $P = 0.008$; respectively). We also found a significant improvement in albumin levels in the "decrease" group (4.00 ±0.61 g/dl vs 4.20 ±0.50 g/dl, $P = 0.0006$). The changes in FTI and TC were nonsignificant.

Survival analysis The all-cause mortality rate was the highest in Q4 (39/81, 48.2%), followed

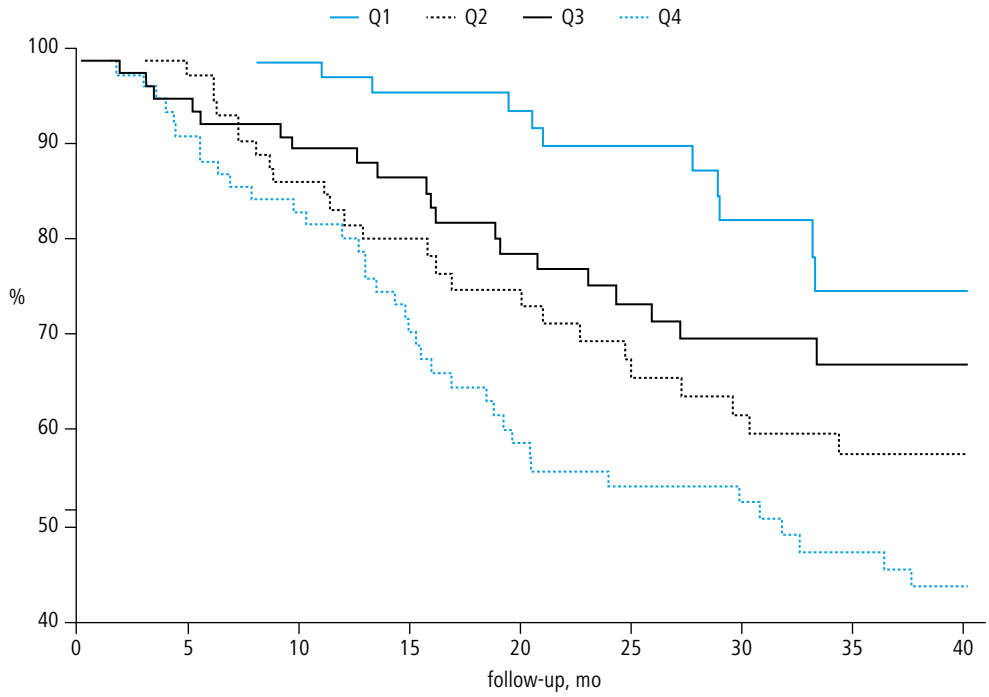

FIGURE 1 Kaplan–Meier survival analysis for the quartiles of N-terminal pro-B-type natriuretic peptide ($P = 0.0001$)

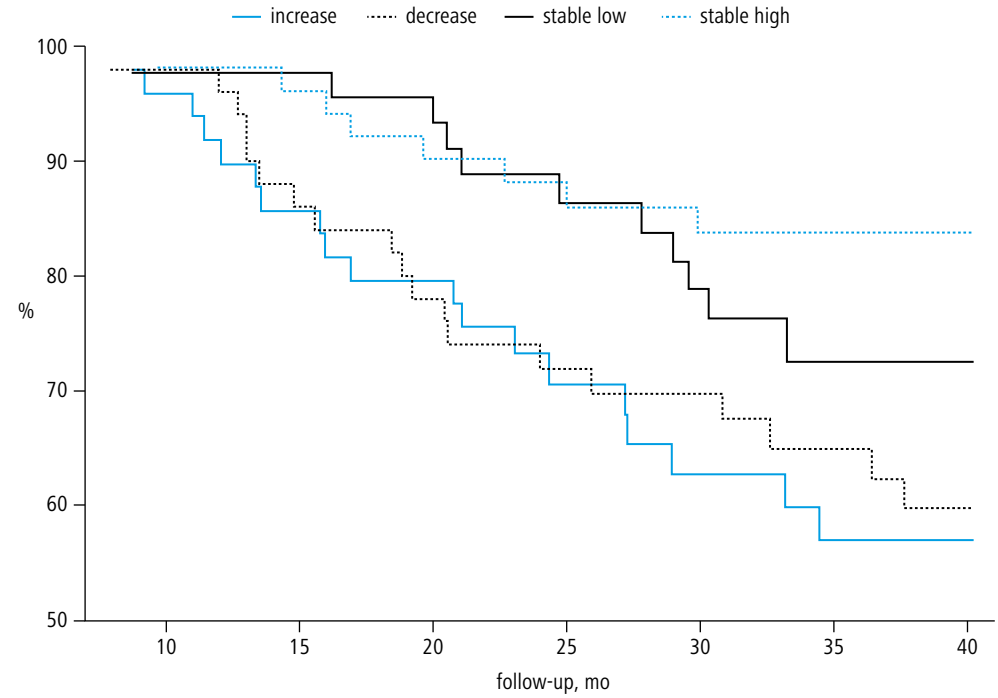

FIGURE 2 Kaplan–Meier survival analysis for the subgroups according to changes in N-terminal pro-B-type natriuretic peptide levels ($P = 0.024$)

by Q2 (26/80, 32.5%), Q3 (21/80, 26.3%), and Q1 (11/80, 13.8%) with a *P* value of less than 0.0001. The differences in CV and non-CV mortality indices were nonsignificant (TABLE 1). The Kaplan–Meier curves for survival probability across the quartiles (FIGURE 1) supported a trend similar to the one already illustrated for all-cause mortality rates. Additionally, FIGURE 2 presents the Kaplan–Meier curves plotted for the subgroups according to changes in NT-proBNP levels, which were strongly in favor of improved survival in the "decrease" and "stable low" groups. The multivariate Cox proportional hazard regression analysis revealed that the NT-proBNP quartile (HR 1.37, $P = 0.005$), ECW/TBW ratio ≥0.503 (HR 1.62, $P = 0.04$), PRDD ≤1000 ml (HR 2.30, $P = 0.003$), and $relOH_{BIA}$ ≥4% (HR, 1.77; $P = 0.01$) were significant unfavorable predictors, while surprisingly, the HD vintage decile (HR, 0.75; $P < 0.0001$) had a protective effect. The results of univariate and multivariate analyses are presented in TABLE 4.

DISCUSSION The results of the current study confirm that NT-proBNP is a marker of hypervolemia in HD patients. We observed an increase in all hydration-related parameters across

TABLE 4 Univariate and multivariate Cox proportional hazard analysis in 321 patients on maintenance hemodialysis

Analysis	Parameter	HR (95% CI)	*P* value	Parameter	HR (95% CI)	*P* value
univariate	ECW/TBW ≥0.503	2.02 (1.31–3.10)	0.001	LTI, kg/m^2	0.92 (0.85–0.99)	0.027
	HD vintage decile	0.79 (0.72–0.86)	<0.0001	history of MI	1.66 (1.04–2.67)	0.035
	NT-proBNP quartile	1.41 (1.17–1.70)	0.0003	BMI, kg/m^2	0.97 (0.93–1.01)	NS (0.17)
	relOH$_{BIA}$ ≥4%	2.11 (1.41–3.15)	0.0003	CRP, mg/l	1.00 (0.997–1.009)	NS (0.33)
	albumin, g/dl	0.50 (0.34–0.73)	0.0004	TC, mg/dl	1.00 (0.99–1.00)	NS (0.52)
	PRDD ≤1000 ml	2.61 (1.54–4.42)	0.0004	diabetes	1.13 (0.74–1.71)	NS (0.58)
	relOH$_{BIA,\%}$	1.13 (1.05–1.21)	0.0005	FTI, kg/m^2	0.99 (0.96–1.03)	NS (0.7)
	absOH$_{BIA}$, l	1.18 (1.07–1.31)	0.0007	history of stroke	1.06 (0.53–2.10)	NS (0.87)
	hemoglobin, g/dl	0.85 (0.75–0.97)	0.02	sex (female)	1.00 (0.66–1.52)	NS (0.99)
multivariate	HD vintage decile	0.75 (0.69–0.82)	<0.0001	relOH$_{BIA}$ ≥4%	1.77 (1.14–2.76)	0.01
	NT-proBNP quartile	1.37 (1.10–1.70)	0.005	ECW/TBW ≥0.503	1.62 (1.02–2.56)	0.04
	PRDD ≤1000 ml	2.30 (1.32–4.00)	0.003			

Abbreviations: CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; others, see **TABLE 1**

the increasing NT-proBNP quartiles, accompanied by several significant correlations between NT-proBNP and those parameters, thus reflecting the effect of fluid overload on NT-proBNP. The monitoring of the hydration status over time also showed that both a decrease and increase in OH was reflected by alterations in NT-proBNP levels. These changes, however, might have been partially influenced by the shifts in residual diuresis (eg, a decrease in PRDD in the "increase" group was associated with an increase in NT-proBNP levels) and with additional unidentified conditions. Our results are in accordance with the observations by other investigators, who either detected significant correlations between NT-proBNP and OH-related parameters (depending on methodology) or high values of natriuretic peptides for patients with fluid overload.[18-28] There are also a number of studies that failed to confirm any relationship between NT-proBNP levels and hydration status, which in some cases might have been due to a low number of studied subjects or the use of different methods.[29-32] Secondly, the fact that many supplementary factors such as blood pressure, dialysis-related parameters, sex, and even age showed no associations with NT-proBNP levels is remarkable. These findings are, at least partially, in line with other studies.[20,24,25,31,32] On the other hand, Booth et al.[21] was able to connect log NT-proBNP with ultrafiltration rate, whereas Nongnuch et al.,[22] Papakrivopoulou et al.,[24] and Yilmaz et al.[26] found substantial correlations between natriuretic peptides and blood pressure. In our study, apart from OH, NT-proBNP was also associated with PRDD, which is not surprising because residual renal function strongly affects NT-proBNP clearance. Furthermore, our data showed that an increase in OH was associated with signs of cardiac muscle damage (cTnT), and that cTnT levels were positively correlated with NT-proBNP and other BIA-derived OH parameters. Other studies that analyzed multiple biomarkers for CV status evaluation support these findings.[18,28,30] Interestingly, we found that a reduction in hypervolemia (and NT-proBNP levels) over time was synchronized with a decrease in myocardial damage indicators and a better prognosis.

The analysis of nutritional and inflammatory parameters gave confounding results. Despite the fact that NT-proBNP correlated negatively with practically all nutritional indices, the distribution of the peak and bottom values in the studied subgroups was uneven. It seems that although our data show a relation of NT-proBNP with nutritional status, this link is less conspicuous than the link between NT-proBNP and OH. Albumin levels, commonly used as a marker of malnutrition, were found to be the lowest for patients with fluid overload by many authors, and this effect is usually linked with dilution.[19] Other investigators also underlined the fact that patients with

low OH and NT-proBNP are usually heavier, with higher levels of fatty tissue and albumin, which is explained by altered fluid distribution mechanisms and is related to reverse epidemiology characteristic for obese HD patients.[22] In general, hemoglobin, albumin, BMI, and FTI were negatively correlated with NT-proBNP, which is in accordance with observations from other studies.[24,29-31]

Intrestingly, the comparisons and correlations for CRP showed no significant results. Although a few studies support our findings,[18,24] the vast majority of investigators managed to connect the inflammatory status with NT-proBNP. It is believed that in patients treated with repeated HD, shifts in intradialytic blood pressures might cause bacterial translocation from the gut to the circulation, which results in secondary endotoxemia and chronic low-grade inflammation.[18] OH, as an underlying cause for gut wall edema, might promote these reactions.[20] In our study, we failed to find any connection between inflammation and hydration status, but since we measured CRP only, our results hardly prove the absence of any relation between these two. The use of interleukin 6 or serum amyloid A might have revealed more interesting results.

NT-proBNP is also believed to be a powerful prognostic indicator. In 2004, Apple et al.[33] first published a paper comparing the use of NT-proBNP and other biomarkers (CRP, cTnT, and cTnI) for survival assessment; as compared to the other biomarkers, NT-proBNP was found to have the largest receiver-operator characteristics area under the curve. The prognostic value of NT-proBNP was confirmed by Sharma et al.[34] in 2006, Madsen et al.[35] and Sommerer et al.[36] in 2007, and many other investigators later on.[17,37-39] The prognostic usefulness of NT-proBNP has also been confirmed in other (nonrenal) groups of patients.[40-42] In our study, the all-cause mortality rates and Kaplan–Meier curves showed that survival was the lowest in Q4 and the highest in Q1 of NT-proBNP. The Cox regression model proved that a transition to a higher NT-proBNP quartile was linked with a 1.36-fold increase in mortality risk. We therefore believe our results to be in line with the observations made by previous investigators. Moreover, a study by Winkler et al.[37] illustrated that patients with more than a double increase in NT-proBNP levels over time had a higher risk of all-cause death than patients with stable levels. Gutierrez et al.[38] investigated the effect of NT-proBNP change during 90 days and found that the group showing an increase in NT-proBNP levels had a 2.4-fold greater risk of all-cause mortality compared with patients with a decrease in NT-proBNP levels. In our cohort, we showed that a stable low value or a decrease in NT-proBNP levels was associated with a better prognosis when compared with patients with an increase in or stable high values of this parameter. However, there are a few interesting issues in terms of survival that require a comment. First, our data showed that despite lower median NT-proBNP levels, the prognosis was worse in Q2 compared with Q3. Intrestingly, the ratio of CV to non-CV mortality in Q2 was 2:1, as compared with the ratio of 1:1 in other quartiles (although the differences in CV and non-CV mortality rates were nonsignificant). We suspect that Q2 subjects were influenced by additional deleterious factors, which were illustrated, at least partially, by slightly lower values of LTI and TC, higher ECW/TBW ratio, as well as longer HD vintage compared with Q3 patients. Secondly, we found significant differences in survival prognosis for patients with stable low and decreasing values of NT-proBNP. We believe this may be explained by the fact that "stable low" patients experienced a drop in hemoglobin levels, while the "decrease" group improved in terms of albumin levels. The above interpretation is highly speculative, and most likely, it does not consider all possible underlying difficulties. Although the assessment of the nutritional status was not the main goal of this study, its influence on survival and prognosis is undeniable.

Some limitations of our study should be acknowledged. Firstly, owing to the design of the study, no conclusions can be made regarding causality. Secondly, the study was conducted in a cohort that was quite homogenous in terms of ethnicity, and the majority of the included patients were Caucasians originating from Poland, restricting its generalizability. Thirdly, image-based diagnostic procedures to assess CV status were lacking; echocardiography and measurement of the intima-media thickness to identify patients with systolic HF and disseminated atherosclerosis, respectively, could have strengthened the study.

In conclusion, natriuretic peptides play a major role in the pathophysiological relationships regulating the CV status in HD patients. NT-proBNP seems to be a valid biomarker of hypervolemia and could represent a valuable tool in the assessment of OH in HD units without access to BIA or other objective techniques. Nevertheless, the assessment of hydration status based on NT-proBNP levels must be interpreted carefully with regard to factors such as the patient's individual residual renal function and CV history. Although the results of the current study are promising, further studies are needed to establish the role of NT-proBNP in everyday clinical practice.

Contribution statement KS, KH, KP, and AO conceived the idea for the study and provided study design. KS, KH, DR, PK, PS, JN, and MK were involved in data collection. JK was involved in blood sample analysis. Data analysis was performed by KS, EB, KP, and BL. AO and KP coordinated funding for the project. All authors edited and approved the final version of the manuscript.

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ARTYKUŁ ORYGINALNY

N-końcowy propeptyd natriuretyczny jako marker przewodnienia i predyktor śmiertelności u pacjentów hemodializowanych

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hemodializa, N-końcowy propeptyd natriuretyczny, powikłania sercowo-naczyniowe, przewodnienie, rokowanie

STRESZCZENIE

WPROWADZENIE N-końcowy propeptyd natriuretyczny (*N-terminal pro-B-type natriuretic peptide* – NT-proBNP) jest uznanym biomarkerem niewydolności serca w populacji ogólnej. Niestety w grupie pacjentów poddawanych hemodializie (HD) jego wartość diagnostyczna jest niejasna ze względu na niewydolność nerek.

CELE Celem badania była ocena przydatności NT-proBNP w ocenie nawodnienia pacjentów HD oraz jego powiązania ze stanem odżywienia i rokowaniem co do przeżycia.

PACJENCI I METODY W grupie 321 pacjentów HD (206 mężczyzn; średnia wieku 65,1 ±21,4 roku) oceniono stężenie NT-proBNP, przewodnienie (OH_{BIA}) i parametry stanu odżywienia (metodą bioimpedancji elektrycznej, BIA) w odniesieniu do poziomu sercowej troponiny T (cTnT), hemoglobiny, albuminy, cholesterolu całkowitego (*total cholesterol* – TC) i białka C-reaktywnego (*C-reactive protein* – CRP). Efektywność HD określono za pomocą Kt/V, tygodniowej dawki HD oraz objętości ultrafiltracji. Kohortę podzielono na kwartyle wg poziomu NT-proBNP. Pacjentów z dwoma pomiarami NT-proBNP skategoryzowano do podgrup w zależności od dynamicznych zmian tego parametru. Mediana obserwacji wynosiła 23,8 ±26,3 miesiąca.

WYNIKI Względne OH_{BIA} wzrastało w poszczególnych kwartylach (Q1/Q2/Q3/Q4: 1,31% ±2,56%/2,06% ±2,35%/2,92% ±2,97%/4,62% ±4,22%; p <0,0001). NT-proBNP było ściśle powiązane również z innymi parametrami nawodnienia. Ponadto stwierdzono istotną korelację między NT-proBNP a cTnT (r = 0,55; p <0,0001). Wskaźnik masy ciała (*body mass index* – BMI) oraz tkanki tłuszczowej (*fat tissue index* – FTI) zmniejszały się w kolejnych kwartylach (BMI: 28,5 ±7,7/26,0 ±6,6/25,8 ±5,4/23,7 ±5,5 kg/m^2; FTI: 14,4 ±9,0/14,1 ±7,3/12,3 ±6,8/11,6 ±6,1; p <0,001). Większe stężenia albuminy obserwowano w Q1 (4,10 ±0,63/3,99 ±0,51/3,90 ±0,62/3,97 ±0,78 g/dl; p = 0,006), TC był najniższy w Q4 (190 ±60/169 ±56/173 ±51/153 ±56 mg/dl; p = 0,002), podczas gdy stężenie hemoglobiny spadało w kolejnych kwartylach (11,44 ±1,25/11,15 ±2,50/10,79 ±1,51/10,45 ±1,67 g/dl; p = 0,0006). Różnice w stężeniu CRP oraz parametrach związanych z HD były nieistotne statystycznie. W trakcie obserwacji zarejestrowano 97 zgonów (11/26/21/39; p <0,0001).

WNIOSKI NT-proBNP jest użytecznym biomarkerem hiperwolemii u pacjentów HD. Niemniej jednak, jego wartości muszą być interpretowane w kontekście resztkowej funkcji nerek oraz stanu układu sercowo-naczyniowego pacjentów.

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