Renal Replacement Therapy

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Range of plasma brain natriuretic peptide (BNP) levels in hemodialysis patients at a high risk of 1-year mortality and their relationship with the nutritional status: a retrospective cohort study in one institute

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Abstract

Background: Brain natriuretic peptide (BNP) levels are used as a marker of heart failure, which is the leading cause of morbidity and mortality in dialysis patients. BNP levels increase as renal function declines. The range of BNP levels associated with satisfactory longevity in dialysis patients currently remains unknown.

Methods: In total, 660 patients receiving maintenance hemodialysis were enrolled. BNP levels were measured at the end of the year and in a follow-up to assess 1-year mortality between 2008 and 2012. Patients were divided into six groups according to BNP levels: < 50 (reference), 50 to < 100, 100 to < 300, 300 to < 500, 500 to < 1000, and ≥ 1000 pg/mL. One-year mortality at each BNP level was analyzed using Cox's proportional hazards model after adjustments for confounding factors.

Results: During the follow-up period, 78 (11.8%) deaths were recorded. After adjustments for confounding factors, such as gender, age, hemodialysis vintage, and primary disease, the risk of 1-year mortality was significantly high with BNP levels of 500 to < 1000 (hazard ratio [HR] 3.010; 95% confidence interval [CI] 1.065–10.729; $P = 0.037$) and more than 1000 pg/mL (HR 5.291; 95%CI 2.014–18.170; $P = 0.0003$). After adjustments for Kt/V, the risk of 1-year mortality was also significantly high with BNP levels of 500 to < 1000 (HR 3.045; 95%CI 1.065–10.929; $P = 0.037$) and more than 1000 pg/mL (HR 5.221; 95%CI 1.943–18.165; $P = 0.0006$). Following further adjustments for nutritional factors, such as albumin levels, total cholesterol levels, the normalized protein catabolic rate (nPCR), body mass index (BMI), and percent creatinine generation rate (%CGR), BNP levels of 500–1000 (HR 1.990; 95%CI 0.639–7.570; $P = 0.244$), and more than 1000 pg/mL (HR 2.100; 95%CI 0.663–8.105; $P = 0.213$) were no longer risk factors.

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(Continued from previous page)
Conclusion: In dialysis patients, a BNP level ≥ 500 pg/mL is a risk factor for 1-year mortality. The risk associated with high BNP levels is reduced by nutritional factors, which suggests a relationship between high BNP levels and the nutritional status. In conclusion, efforts are needed to maintain BNP levels at lower than 500 pg/mL and improve the nutritional status.

Keywords: Brain natriuretic peptide, Hemodialysis, Mortality, Nutritional status

Background

Brain natriuretic peptide (BNP) levels are used as a marker of heart failure [1], which is the leading cause of morbidity and mortality in hemodialysis patients. BNP levels in these patients are crucial for diagnosing and assessing the severity of heart failure and predicting future cardiovascular morbidity and mortality [2]. Plasma BNP levels increase with declines in renal function, and BNP levels are elevated in hemodialysis patients, even in the absence of heart failure. However, the normal threshold of BNP levels in hemodialysis patients currently remains unknown.

The range of BNP levels in hemodialysis patients needs to be clarified in order to ensure satisfactory longevity. Therefore, the present study investigated the relationship between plasma BNP levels and 1-year mortality in hemodialysis patients and examined the range of BNP levels associated with an improved prognosis.

Methods

In total, 660 patients receiving maintenance hemodialysis were enrolled in the present study. BNP levels were measured at the end of the year and in a follow-up to assess 1-year mortality between 2008 and 2012. The hazard ratio (HR) for 1-year mortality was evaluated in six groups of patients divided according to BNP levels: BNP < 50 (control), 50 ≤ BNP < 100, 100 ≤ BNP < 300, 300 ≤ BNP < 500, 500 ≤ BNP < 1000, and 1000 ≤ BNP. Analyses were performed in four steps. In the first step, we adjusted for basal confounding factors, such as gender, age, hemodialysis vintage, and primary disease. In the second step, we adjusted for Kt/V as a prescriptive factor. In the third step, we adjusted for nutritional factors, including serum albumin levels, total cholesterol levels, the normalized protein catabolic rate (nPCR), body mass index (BMI), and percent creatinine generation rate (%CGR). In the fourth step, we adjusted for transthyretin (also known as prealbumin) levels.

A blood sample was obtained before the first hemodialysis session of the week. BNP levels were measured using the automatic enzyme immunoassay device AIA-600II® (TOSO CORPORATION) with E-test TOSO II (BNP).

All statistical analyses were performed using JMP (ver.10). *P* values less than 0.05 were considered to be significant.

The present study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Research Ethics Committee of Kenwakai Hospital (No. 2019008).

Results

The baseline characteristics of study participants are shown in Table 1 . Among 660 patients, 446 (67.6%) were male. As the primary disease, 318 (48.2%) had chronic glomerulonephritis (CGN), 255 (38.6%) diabetic nephropathy (DN), and 87 (13.2%) other diseases. Regarding patient characteristics related to heart disease, 578 (87.6%) out of 660 patients were prescribed antihypertensive agents, while 147 (22.3%) had a history of acute coronary syndrome, coronary intervention, or coronary surgery. Aortic stenosis and/or regurgitation of more than moderate severity according to the ACC/AHA practice guidelines were noted in 40 (6.2%) out of 645 patients examined by echocardiography. Mitral regurgitation of more than moderate severity and/or severe was detected in 26 (4.0%) out of 645 patients examined by echocardiography. Heart failure with a reduced ejection fraction (< 40%) was observed in 18 (2.80%) out of 641 patients examined by echocardiography. The most common hemodialysis vintage was 5–10 (29.7%). As a hemodialysis prescription factor, Kt/V values were the most frequently distributed between 1.4 and < 1.6 (30.6%). Nutritional factors were nPCR, serum albumin levels, total cholesterol levels, BMI, and %CGR. In the analysis of targeting factors, 147 patients had a BNP level of 100 to < 200 pg/mL (22.3%), and 143 had a transthyretin level of 20 to < 25 mg/dL (21.8%). As shown in Table 2 , the mean age was 68.5 ± 12.9 years and mean vintage was 6.48 ± 5.09 years.

Table 3 shows the prognosis of study participants. During the observation period, there were 78 deaths (11.8%). Table 4 shows the causes of death: heart failure in 19, cerebrovascular disease in 13, infection in 11, cachexia/uremia in 10, sudden death in 6, malignant tumors in 5, gastrointestinal disease in 5, and myocardial infarction in 4. Table 5 shows HR for 1-year mortality after adjustments for confounding factors. DN as the primary disease was a significantly higher risk factor (HR 2.11; 95%CI 1.31–3.45; P = 0.0018) than CGN. Kt/V

Table 1 Background characteristics of the study participants

Basal factors										
Gender	**male**	**female**	**total**							
Number	446	214	660							
%	67.6	32.4	100							
Age (year)	**0~**	**30~**	**45~**	**60~**	**75~**	**total**				
Number	6	24	115	285	230	660				
%	1	3.6	17.4	43.2	34.8	100				
Primary disease	**CGN**	**DM**	**others**	**total**						
Number	318	255	87	660						
%	48.2	38.6	13.2	100						
Hemodialysis vintage	**< 2**	**2~**	**5~**	**10~**	**15~**	**20~**	**25~**	**≥ 30**	**total**	
Number	136	186	196	91	39	10	2	0	660	
%	20.6	28.2	29.7	13.8	5.9	1.5	0.3	0	100	
Hemodialysis prescription factor										
Kt/V	**<0.8**	**0.8~**	**1.0~**	**1.2~**	**1.4~**	**1.6~**	**1.8~**	**≥ 2.0**	**total**	
Number	13	20	47	110	202	152	75	41	660	
%	2	3	7.1	16.7	30.6	23	11.4	6.2	100	
Nutrition factors										
nPCR (g/kg/day)	**<0.5**	**0.5~**	**0.7~**	**0.9~**	**1.1~**	**≥ 1.3**	**total**			
Number	21	175	320	124	17	2	660			
%	3.2	26.6	48.5	18.8	2.6	0.3	100			
Albumin (g/dl)	**<3.0**	**3.0~**	**3.5~**	**4.0~**	**≥ 4.5**	**total**				
Number	49	235	306	69	1	600				
%	7.4	35.6	46.4	10.5	0.1	100				
BMI (kg/m^2)	**<16**	**16~**	**18~**	**20~**	**22~**	**24~**	**26~**	**≥ 28**	**total**	
Number	5	32	120	186	156	93	31	36	660	
%	0.7	4.9	18.2	28.2	23.7	14.1	4.7	5.5	100	
Total cholesterol (mg/dl)	**<80**	**80~**	**120~**	**160~**	**200~**	**≤ 240**	**total**			
Number	0	68	283	193	31	1	576			
%	0	11.8	49.1	33.5	5.4	0.2	100			
%CGR (%)	**<60**	**60~**	**70~**	**80~**	**90~**	**100~**	**110~**	**120~**	**≥130**	**total**
Number	66	48	78	95	110	115	71	38	35	656
%	10.1	7.3	11.9	14.5	16.8	17.5	10.8	5.8	5.3	100
Analysis targeting factors										
BNP (pg/ml)	**<50**	**50~**	**100~**	**200~**	**300~**	**500~**	**≥ 1000**	**total**		
Number	97	99	147	62	79	92	84	660		
%	14.7	15	22.3	9.4	12	13.9	12.7	100		
Transthyretin (mg/dl)	**<15**	**15-20**	**20-25**	**25-30**	**30-35**	**35-40**	**≥ 40**	**total**		
Number	32	60	143	141	130	92	59	657		
%	4.9	9.1	21.8	21.4	19.8	14	9	100		

values of 1.0 to < 1.2 were a significantly higher risk factor than 1.2 to < 1.4 (HR 2.42; 95%CI 1.12–5.18; $P = 0.02$). N-PCR values of 0.5 to < 0.7 were a significantly higher risk factor than 0.7 to < 0.9 (HR 2.07; 95%CI 1.26–3.42; $P = 0.0039$). Serum albumin levels of 3.0 to < 3.5 g/dL were a significantly higher risk factor (HR 3.25; 95%CI 1.87–5.88; $P < 0.0001$) than 3.5 to < 4.0 g/dL. %CGR of 60–70% was a significantly higher risk factor than 90 to < 100% (HR 2.75; 95%CI 1.11–9.92; $P < 0.030$). Transthyretin levels of 15 to < 20 mg/dL were a significantly higher

Table 2 Mean values of factors in study participants

Factor	Number	Mean ± SD
Age	660	68.5 ± 12.9
Hemodialysis vintage (year)	660	6.48 ± 5.09
Kt/V	660	1.533 ± 0.343
nPCR (g/kg/day)	659	0.782 ± 0.157
Albumin (g/dl)	660	3.49 ± 0.412
BMI (kg/m^2)	656	22.21 ± 3.06
Total cholesterol (mg/dl)	576	153.04 ± 29.14
%CGR (%)	656	92.1 ± 24.93
BNP (pg/mL)	660	480.02 ± 732.01

BMI body mass index, *BNP* brain natriuretic peptide, *nPCR* normalized protein catabolic rate, *%CGR* percent creatinine generation rate

risk factor than 20 to < 25 mg/dL (HR 3.86; 95%CI 1.92–8.00; $P = 0.0002$).

Figure 1 shows the results obtained in the Kaplan-Meier survival analysis of BNP levels. The 1-year survival rate was significantly low at a BNP level > 300 pg/mL. Figure 2 shows the estimated cubic spline transformation of the relationship between BNP levels and HR for 1-year mortality adjusted for age, gender, dialysis vintage, and primary diseases. BNP levels in hemodialysis patients correlated with 1-year mortality. Figure 3 shows a receiver operating characteristic (ROC) curve of the relationship between BNP levels and 1-year mortality. The area under the curve was 0.69, and the cut-off value was 299.2 pg/mL. Table 6 shows HR for 1-year mortality at each BNP level relative to that less than 50 pg/mL. After adjustments for basal confounding factors (gender, age, primary disease, and hemodialysis vintage) (model 1), comparisons with the reference group revealed that BNP levels of 500 to < 1000 pg/mL were a significantly high-risk factor (HR 3.01; 95%CI 1.07–10.73; $P < 0.037$), as were those higher than 1000 pg/mL (HR 5.29; 95%CI 2.01–18.17; $P < 0.0003$). After further adjustments for Kt/V values (model 2), similar results were obtained to those in model 1. A BNP level higher than 500 pg/mL was significantly high. After further adjustments for five nutritional factors (nPCR, serum albumin levels, BMI, total cholesterol levels, and %CGR) (model 3), BNP levels higher than 500 pg/mL were not significant. Table 7 also shows HR for 1-year mortality at each BNP level. Models 1 and 2 were the same as those in Table 6, whereas model 4 showed HR further adjusted for transthyretin. BNP levels higher than 500 pg/mL were also not significant.

Table 3 Prognosis of study participants

Prognosis	Number	%
Survival	582	88.2
Death	78	11.8
Total	660	100

Table 4 Causes of death

	Number	%
Heart failure	19	24.3
Cerebrovascular disease	13	16.7
Infection	11	14.1
Cachexia/uremia	10	12.8
Sudden death	6	7.7
Malignant tumor	5	6.4
Gastrointestinal disease	5	6.4
Myocardial infarction	4	5.1
Others	5	6.4
Total	78	100

Table 8 shows correlation coefficients and *P* values for BNP and each parameter. BNP levels correlated with age, BMI, albumin levels, total cholesterol levels, Kt/V, nPCR, %CGR, and transthyretin levels. BNP levels showed the strongest correlation with transthyretin levels.

Discussion

The Japanese Society for Dialysis Treatment (JSDT) investigated several indices related to 1-year mortality in patients after adjustments for basal confounding factors, including gender, age, hemodialysis vintage, and primary disease; dialysis prescription factors, such as Kt/V; and nutritional factors, including nPCR, albumin levels, total cholesterol levels, BMI, and %CGR [3]. BNP levels were not included in these indices. In the present study, we used the JSDT method to analyze HR for 1-year mortality at different BNP levels. We concluded that a BNP level higher than 500 pg/mL is a significantly high-risk factor for 1-year mortality.

The present study confirmed previous findings showing that BNP levels are a predictor of mortality in hemodialysis patients [4–6]. Naganuma et al. reported that a BNP level less than 200 pg/mL was associated with a good prognosis after a 3-year follow-up [7], whereas Biasioli et al. showed that a BNP level less than 335 pg/mL was associated with a good prognosis after a 28-month follow-up [8]. Zoccali et al. identified a BNP level higher than 125 pg/mL as a significantly high-risk factor after a 26-month follow-up [9, 10]. Our follow-up period of 1 year was the shortest, while the number of factors used for adjustments was the largest. A shorter follow-up period is suitable for evaluating BNP levels as a tool for risk stratification and treatment guidance. BNP levels need to be maintained at lower than 500 pg/mL as a daily management goal.

Table 5 Cox's proportional hazard ratio of prognostic correcting factors

factor	Hazard ratio	95%CI		p value
		lower	upper	
Basal correcting factors				
Gender				
male (reference)	1			
female	0.8071195	0.482928	1.301835	0.3874
Age				
per year	1.080624	1.056946	1.105951	0.925391
Hemodialysis vintage(year)				
<2	1.2368068	0.676626	2.236559	0.4845
2~	0.9264575	0.511665	1.664664	0.7981
5~ (reference)	1			
10~	0.6188481	0.246238	1.363282	0.2444
15~	0.835351	0.245519	2.161668	0.7336
20~	0.8217469	0.045988	3.884436	08428
25~	6.6119647	0.369841	31.30687	0.1522
30~	-	-	-	-
Primary disease				
CGN (reference)	1			
DN	2.1136519	1.317961	3.452752	0.0018
others	0.9470856	0.379865	2.057472	0.8975
Hemodialysis prescription factor				
Single pool Kt/V				
<0.8	3.4472538	1.113841	9.013165	0.0336
0.8 to <1.0	1.3144702	0.303081	4.027443	0.6766
1.0 to <1.2	2.4205658	1.123396	5.178495	0.0246
1.2 to <1.4 (reference)	1			
1.4 to <1.6	0.9066037	0.472084	1.805214	0.7733
1.6 to <1.8	0.6185594	0.281182	1.339853	0.2214
1.8 to <2.0	0.4126628	0.116978	1.150472	0.0935
2.0≦	0.7575922	0.214755	2.1121	0.6157
Nutrition relating factors				
nPCR (g/kg/day)				
<0.5	3.5341434	1.326819	791195	0.0144
0.5 to <0.7	2.0793417	1.267456	3.424633	0.0039
0.7 to <0.9 (reference)	1			
0.9 to <1.1	0.6749971	0.288367	1.402628	0.3057
1.1 to <1.3	2.11E-09	0	1.180454	0.0706
1.3≦	2.11E-09	0	10.03386	0.5302
Albumin (g/dl)				
<0.3	8.9979761	4.666076	17.49091	<.0001
3.0 to <3.5	3.2500965	1.875694	5.882808	<.0001
3.5 to <4.0 (reference)	1			
4.0 to <4.5	0.5191474	0.0082335	1.810644	0.3393
4.5≦	3.22E-08	0	35.6988	0.7359
Total cholesterol (mg/dl)				
<80	-	-	-	-
80 to <120	1.3127943	0.637005	2.493205	0.441
120 to <160 (reference)	1			
160 to <200	0.7676479	0.431736	1.321843	0.3451
200 to <240	0.7481263	0.180457	2.071826	0.6148
240≦	77.12728	4.101126	441.142	0.0104
BMI (kg/m^2)				
<16	2.6829842	0.593253	12.33062	0.1361
16 to <18	1.4307039	0.532743	3.250588	0.4465
18 to <20	0.764411	0.380715	1.460268	0.4227
20 to <22 (reference)	1			
22 to <24	0.7607745	0.405455	1.390405	0.3769
24 to <26	0.6119119	0.258927	1.292297	0.206
26 to <28	0.2169053	0.012157	1.01973	0.0538
28≦	0.7508242	0.221565	1.927202	0.5806
%CGR (%)				
<60	3.5766971	1.630619	8.3974	0.0014
60 to <70	2.7486736	1.107819	6.919564	0.0297
70 to <80	1.4473888	0.56513	3.706997	0.4341
80 to <90	1.4485841	0.599571	3.593324	0.4081
90 to <100 (reference)	1			
100 to <110	1.166507	0.482823	2.893589	0.7313
110 to <120	0.508935	0.112931	1.705797	0.287
120 to <130	0.6324356	0.096427	2.454098	0.5391
130≦	1.059352	0.235067	3.550648	0.9314
Transthyretin (mg/dl)				
<15	10.055064	4.997492	20.87464	<.0001
15 to <20	3.8640013	1.924016	8.008218	0.0002
20 to <25 (reference)	1			
25 to <30	1.089919	0.509545	2.348036	0.823
30 to <35	0.759041	0.313215	1.759291	0.5221
35 to <40	0.350335	0.080339	1.086928	0.0712
40≦	5.23E-10	0	0.368802	0.0023

BMI body mass index, *CGN* chronic glomerulonephritis, *DN* diabetic nephropathy, *nPCR* normalized protein catabolic rate, *%CGR* percent creatinine generation rate

The risk associated with a BNP level ≥ 500 pg/mL was canceled after adjustments for nutritional factors. Therefore, a relationship appears to exist between high BNP levels and the nutritional status. The presence of chronic heart failure with ongoing weight loss or a low BMI is a

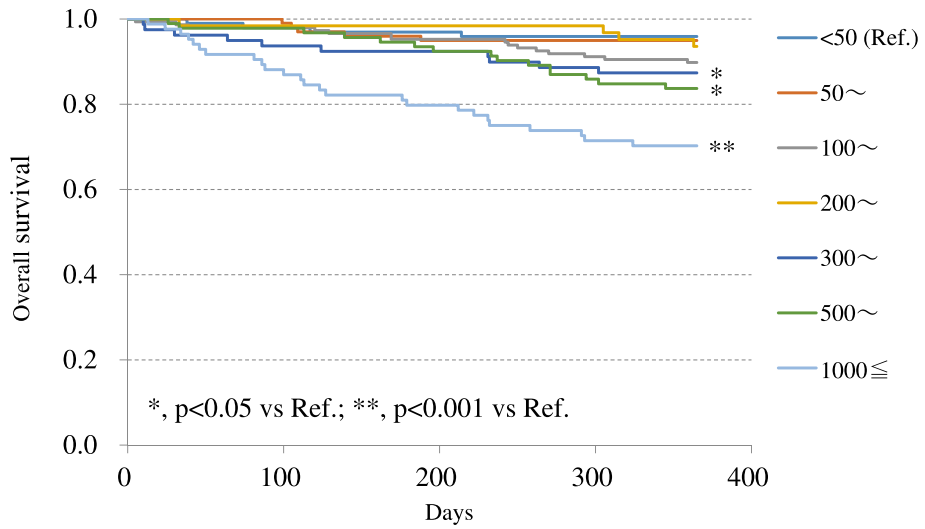

Fig. 1 Kaplan-Meier survival analysis of BNP levels. One-year survival rates were 95.5% at BNP <50 pg/mL, 95.0% at 50-100 pg/mL, 90.0% at 100-200 pg/mL, 93.6% at 200-300 pg/mL, 87.3% at 300-500 pg/mL, 83.7% at 500-1000 pg/mL, and 70.2% at >1000 pg/mL. The 1-year survival rate was significantly low at BNP >300 pg/mL

predictor of muscle mass loss, a decline in exercise capacity, and a poor prognosis [11]. A syndrome involving weight loss, general fatigue, fat loss, and muscle wasting with chronic disease was recently recognized as cachexia. Cachexia is a prevalent and important pathological condition associated with chronic heart failure. It reduces survival independently of the heart failure function class and ejection [12, 13]. BNP levels play a major role in salt and water homeostasis, protecting the cardiovascular system from the effects of volume overload and cardiac comorbidities. In the bioimpedance method, BNP levels reflect individual variations in the hydration status of hemodialysis patients [14]. A value of 500 pg/mL has been used to differentiate between hemodialysis patients with or without volume overload [15, 16]. The extracellular water content to intracellular water content ratio increases as BMI decreases. A strong negative correlation was previously reported between excess fluid mass and BMI [17]. Patients with BNP levels higher than 500 pg/mL were overhydrated and weight loss from

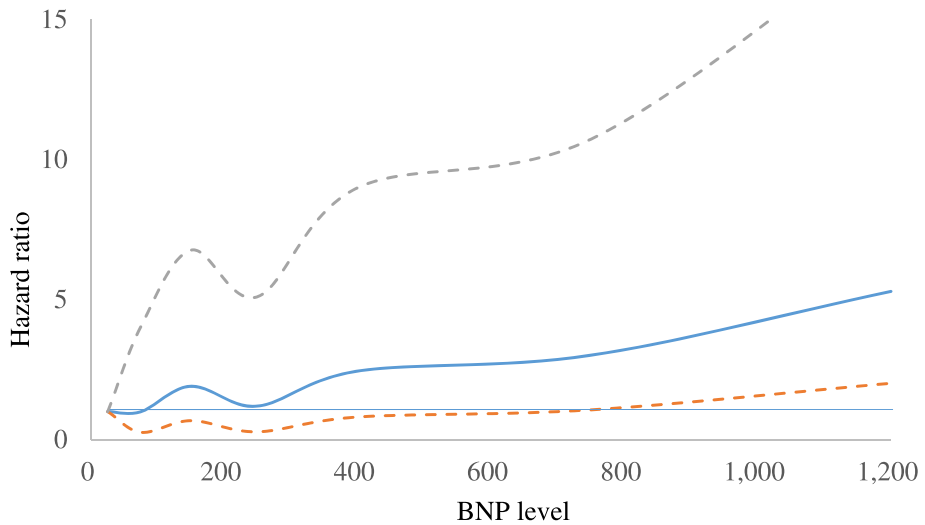

Fig. 2 Estimated cubic spline transformation of the relationship between BNP levels and the adjusted hazard ratio. The reference BNP for this plot (with HR fixed as 1.0) was <50 pg/mL. The hazard ratio of 1-year mortality was adjusted for age, gender, dialysis vintage, and primary diseases. Dotted lines are 95% confidence limits

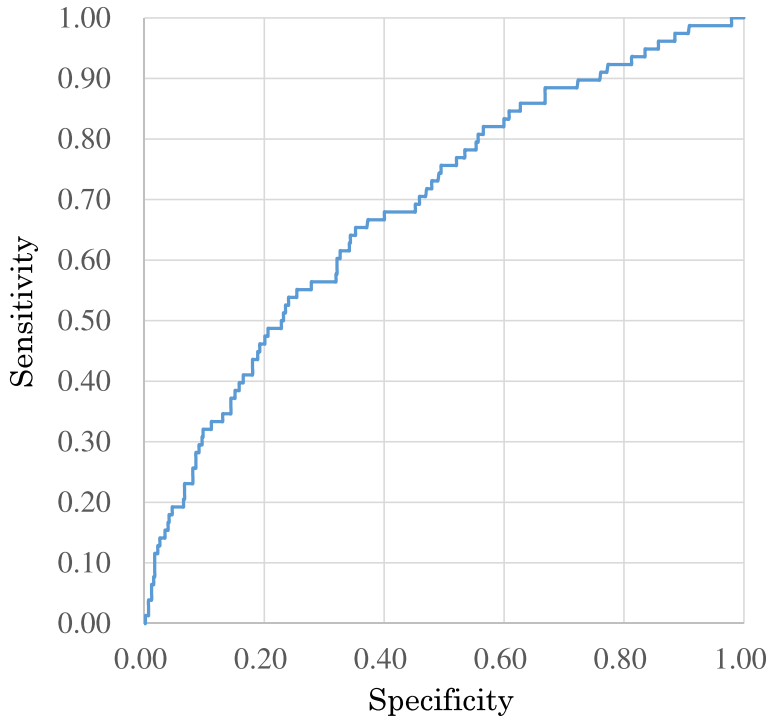

Fig. 3 Receiver operating characteristic (ROC) curve of the relationship between BNP levels and 1-year mortality. The area under the curve was 0.69 and the cut-off value was 299.2 pg/mL

malnutrition resulted in additional fluid excess. On the other hand, even though BNP levels were high, good nutrition, and weight gain reduced volume overload. Chronic overhydration is an independent predictor of mortality in hemodialysis patients [18]. The risk associated with a high BNP level depends on the nutritional status. The combination of a high BNP level with a poor nutritional status needs to be treated not only by cardiological therapy, but also nutritional support. Despite the accepted importance of the influence of nutritional factors on the severity of cardiovascular disease, limited information is currently available on dietary intake and heart failure. Furthermore, existing nutritional interventions for heart failure were mostly pilot studies with small sample sizes and short follow-ups [19]. The findings of 17 randomized controlled trials indicated that education on nutritional interventions had positive effects on the clinical outcomes of patients; however, they

Table 6 HR for 1-year mortality of BNP levels adjusted for basal factors, Kt/V and nutrition factors

BNP (pg/ml)	Adjusted for basal factors (model 1)				Adjusted for basal factors and Kt/V (model 2)				Adjusted for basal factors, Kt/V and nutrition factors (model 3)			
	HR	p value	95%CI		HR	p value	95%CI		HR	p value	95%CI	
			lower	upper			lower	upper			lower	lower
<50 (reference)	1	-	-	-	1	-	-	-	1	-	-	-
50 to <100	0.997121	0.9966	0.262147	4.051568	0.964564	0.9574	0.253041	3.926629	0.8384388	0.8047	0.205753	3.621547
100 to <200	1.907679	0.2326	0.678499	6.766743	1.840871	0.2619	0.652984	6.541653	0.9592779	0.9477	0.292026	3.725938
200 to <300	1.198396	0.7993	0.28121	5.106865	1.165241	0.8354	0.260802	5.155792	0.8387627	0.8229	0.170045	4.04536
300 to <500	2.446838	0.1157	0.808727	8.994658	2.5366	0.1026	0.835008	9.354117	2.5461197	0.133	0.758488	10.11498
500 to <1000	3.009917	**0.0369**	1.065084	10.72921	3.044996	**0.037**	1.065717	10.92917	1.9907521	0.2444	0.639274	7.570738
≥1000	5.291238	**0.0003**	2.013968	18.17073	5.221112	**0.0006**	1.943194	18.16484	2.0999726	0.2136	0.663497	8.104608

HR hazard ratio

Table 7 HR for 1-year mortality of BNP levels adjusted for basal correcting factors, Kt/V and transthyretin

BNP (pg/ml)	Adjusted for basal factors (model 1)				Adjusted for basal factors and Kt/V (model 2)				Adjusted for basal factors, Kt/V and transthyretin (model 4)			
	HR	p value	95%CI		HR	p value	95%CI		HR	p value	95%CI	
			lower	upper			lower	upper			lower	lower
<50 (reference)	1	-	-	-	1	-	-	-	1	-	-	-
50 to <100	0.997121	0.9966	0.262147	4.051568	0.964564	0.9574	0.253041	3.926629	0.8926795	0.8672	0.233334	3.644237
100 to <200	1.907679	0.2326	0.678499	6.766743	1.840871	0.2619	0.652984	6.541653	1.7642041	0.3025	0.619779	6.310716
200 to <300	1.198396	0.7993	0.28121	5.106865	1.165241	0.8354	0.260802	5.155792	0.8019716	0.7659	0.178553	3.594217
300 to <500	2.446838	0.1157	0.808727	8.994658	2.5366	0.1026	0.835008	9.354117	1.986255	0.2446	0.636523	7.46915
500 to <1000	3.009917	**0.0369**	1.065084	10.72921	3.044996	**0.037**	1.065717	10.92917	1.7769718	0.3121	0.602509	6.532927
≥1000	5.291238	**0.0003**	2.013968	18.17073	5.221112	**0.0006**	1.943194	18.16484	2.710241	0.0653	0.942719	9.854096

HR hazard ratio

all involved sodium and fluid restrictions [20]. After the administration of a high-caloric (600 kcal), high-protein (20 g), and oral nutritional supplement for 6 weeks to cachexic heart failure patients, significant improvements were observed in the quality of life, 6-m walking test, and tumor necrosis factor-α without the significant recovery of peak VO_2 or the left ventricular ejection fraction; BNP was not measured in that study [21]. After the administration of 500 mL/day of enteral nutrition for 3 months to elderly heart failure patients, marked improvements were noted in BNP, interleukin-6, tumor necrosis factor-α, and C-reactive protein levels [22].

After adjustments for transthyretin levels, the risk associated with BNP ≥ 500 pg/mL was no longer significant. Transthyretin is an important indicator of not only the nutritional status, but also the survival of hemodialysis patients after adjustments for age, gender, race, hemodialysis vintage, the diabetic state, and nutritional markers, including serum albumin levels [22, 23]. A recent study reported that serum transthyretin levels correlated with body fat mass [24]. The half-life of transthyretin is 2–3 days, which is shorter than that of serum albumin. A decline in serum transthyretin levels by 10 g/dL over 6 months is a robust predictor of increased mortality [25, 26]. The present results showed that a transthyretin level of less than 20 mg/dL was a high-risk factor. In hemodialysis patients, the combination of a BNP level ≥ 500 pg/mL and transthyretin level < 20 mg/dL, which is a decrease of more than 10 mg, warrants urgent treatment.

Table 8 Correlation coefficients and p value for BNP and the studied parameter

	Mean	SD	r	p
Age	68.51212	12.86282	0.222574	<.0001
Hemodialysis vintage (year)	6.476169	5.092643	0.017756	0.6489
BMI (kg/m^2)	22.2116	3.056318	-0.14469	0.0002
Albumin (g/dl)	3.490455	0.4122	-0.29155	<.0001
Total cholesterol (mg/dl)	153.0382	29.14238	-0.11052	0.0079
Kt/V	1.532889	0.342536	-0.1803	<.0001
nPCR (g/kg/day)	0.782168	0.15667	-0.19454	<.0001
%CGR (%)	92.01985	24.93402	-0.21274	<.0001
Transthyretin (mg/dl)	28.45586	8.384788	-0.39012	<.0001

BMI body mass index, *nPCR* normalized protein catabolic rate, *%CGR* percent creatinine generation rate

Conclusions

In dialysis patients, a BNP level ≥ 500 pg/mL is a significantly high-risk factor for 1-year mortality. The risk associated with a high BNP level is canceled out after adjustments for nutritional factors. Therefore, a relationship appears to exist between high BNP levels and the nutritional status. Efforts are needed to maintain a BNP level of less than 500 pg/mL and improve nutritional factors. The risk associated with a BNP level ≥ 500 pg/mL also depends on transthyretin levels, which need to be maintained at > 20 mg/dL.

Abbreviations

%CGR: Percent creatinine generation rate; BMI: Body mass index; BNP: Brain natriuretic peptide; CGN: Chronic glomerulonephritis; DN: Diabetic nephropathy; nPCR: Normalized protein catabolic rate

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Authors' contributions

EK wrote the manuscript and KH revised it. EK contributed to the research concept and study design. KF contributed to data acquisition, the risk of bias assessment, data analysis/interpretation, and statistical analyses. ST contributed to data interpretation. EK contributed to supervision and mentorship. The authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this manuscript.

Ethics approval and consent to participate
The present study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the research Ethics Committee of Kenwakai Hospital (No.2019008).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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