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Clinical efficacy of biomarkers for evaluation of volume status in dialysis patients

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Abstract

Volume status is a key parameter for cardiovascular-related mortality in dialysis patients. Although N-terminal pro-B-type natriuretic peptide (NT-proBNP), myeloperoxidase, copeptin, and pro-adrenomedullin have been reported as volume markers, the relationship between body fluid status and volume markers in dialysis patients is uncertain. Therefore, we investigated the utility of volume status biomarkers based on body composition monitor (BCM) analyses.

We enrolled pre-dialysis, hemodialysis (HD), and peritoneal dialysis (PD) patients and age- and gender-matched healthy Korean individuals (N = 80). BCM and transthoracic echocardiography were performed and NT-proBNP, myeloperoxidase, copeptin, and pro-adrenomedullin concentrations were measured. Relative hydration status (ΔHS, %) was defined in terms of the hydration status-to-extracellular water ratio with a cutoff of 15%, and hyperhydrated status was defined as ΔHS > 15%.

Although there were no significant differences in total body water, extracellular water, or intracellular water among groups, mean amount of volume overload and hyperhydrated status were significantly higher in HD and PD patients compared with control and pre-dialysis patients. Mean amount of volume overload and hyperhydrated status were also significantly associated with higher NT-proBNP and pro-adrenomedullin levels in HD and PD patients, although not with myeloperoxidase or copeptin levels. Furthermore, they were significantly associated with cardiac markers (left ventricular mass index, ejection fraction, and left atrial diameter) in HD and PD patients compared with those in the control and pre-dialysis groups.

On the basis of increased plasma NT-proBNP and pro-adrenomedullin concentrations, we might be able to make predictions regarding the volume overload status of dialysis patients, and thereby reduce cardiovascular-related mortality through appropriate early volume control.

Abbreviations: BCM = body composition monitor, ESRD = end-stage renal disease, HD = hemodialysis, hs-CRP = high-sensitivity C-reactive protein, LV = left ventricular, NT-proBNP = N-terminal pro-B-type natriuretic peptide, PD = peritoneal dialysis.

Keywords: cardiovascular disease, hemodialysis, N-terminal pro-B-type natriuretic peptide (NT-proBNP), peritoneal dialysis, pro-adrenomedullin, volume

1. Introduction

Chronic volume overload is associated with systemic hypertension, increased left ventricular hypertrophy, and cardiovascular-related mortality.[1] Cardiovascular complications are the main cause of death in end-stage renal disease (ESRD) patients on dialysis. Most of the recent advances in identifying the causes of cardiovascular complications related to ESRD have tended to focus on atherosclerosis and mechanisms related to hemodynamic change.[2] In this regard, it is important to make accurate assessments of fluid status in dialysis patients. Moreover, control of extracellular volume is considered a key measure for reducing hypertension and the incidence of cardiovascular-related mortality in these patients.[3]

Editor: Jinxian Xu.

Compliance with ethical standards

Informed consent: Informed consent was obtained from all individual participants included in the study.

Ethical standards: All procedures performed in studies involving human participants were in accordance with the ethical standards of the Human Subjects Institutional Review Board of the Inje University Haeundae Paik Hospital (2012–057)) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files]. The authors have no funding.

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How to cite this article: Park WY, Park S, Kim YW, Jin K. Clinical efficacy of biomarkers for evaluation of volume status in dialysis patients. Medicine 2020;99:31 (e21460).

Received: 13 November 2019 / Received in final form: 9 June 2020 / Accepted: 26 June 2020

http://dx.doi.org/10.1097/MD.0000000000021460

Measurements of intracellular and extracellular fluid volumes may contribute to detecting volume overload and to enabling definition of an optimal dry weight in dialysis patients.[3] Several objective methods have been proposed to facilitate the correct estimation of dry weight in dialysis patients, including ultrasound monitoring of the inferior vena cava and lungs, radionuclide dilution techniques, and echocardiography.[4] However, these methods are either time-consuming or difficult to perform. As an alternative, the bioimpedance spectroscopic method has been validated by isotope dilution methods, accepted reference body composition methods, techniques that measure relative changes in fluid volumes, and extensive clinical assessment of the hydration state.[5] The body composition monitor (BCM: Fresenius Medical Care, Bad Homburg, Germany) is a portable whole-body multi-frequency bioimpedance analysis device that can be used to perform simple bedside measurements of the body composition and hydration status of patients.[6] Using this device, measurements of relative volume overload of >15% are considered indicative of an increased risk of cardiovascular-related mortality.[5]

Numerous molecular markers have been reported to be associated volume status, among which, N-terminal pro-B-type natriuretic peptide (NT-proBNP), myeloperoxidase, copeptin, and pro-adrenomedullin have been shown to be volume markers related to heart failure and hypertension.[7–11] NT-proBNP is a marker of both fluid volume overload and myocardial damage, and plasma levels of this natriuretic peptide have also been found to be directly associated with left ventricular mass and fluid volume overload.[12–16] Myeloperoxidase is a pro-oxidant enzyme associated with an increased susceptibility to cardiovascular disease. Several studies have demonstrated that the plasma levels of myeloperoxidase have an independent and prognostic cardiovascular value with respect to heart failure patients.[17–19] Furthermore, copeptin, the carboxy-terminal portion of the precursor of arginine vasopressin, has been shown to be a reliable surrogate marker of circulating arginine vasopressin concentrations.[20,21] Adrenomedullin, along with its precursor pro-adrenomedullin, is synthesized and present in the adrenal glands, heart, lungs, blood vessels, and kidneys.[8] It is a potent vasodilator with inotropic and natriuretic properties and its production is stimulated by volume overload.[22] Although these cardiac biomarkers are related to mortality in individuals with congestive heart failure, whether they could serve as predictors of volume status in ESRD patients remains unknown.

In this study, we sought to examine the body composition of dialysis patients and to evaluate the efficacy of relevant biomarkers for optimized fluid balance in these patients.

2. Methods

2.1. Study population

As the study population for the present investigation, we enrolled 20 hemodialysis (HD) patients (12 men and 8 women aged 47.4 ± 12.6 [SD] years), 20 peritoneal dialysis (PD) patients (12 men and 8 women aged 48.6 ± 7.6 years), and 20 chronic kidney disease patients without dialysis (pre-dialysis) (12 men and 8 women aged 48.1 ± 14.3 years). The underlying causes of kidney disease in the HD group were as follows: diabetes mellitus in 12 patients; hypertension in six; and chronic glomerulonephritis in two. The underlying causes of kidney disease in the PD group were diabetes mellitus in 12 patients, hypertension in five, and chronic glomerulonephritis in three. The underlying causes of kidney disease in the pre-dialysis group were diabetes mellitus in eight patients, hypertension in six, and chronic glomerulonephritis in six. In addition to these 60 patients, we recruited 20 apparently healthy individuals (11 men and 9 women; mean age, 45.7 ± 6.4 years) to serve as controls.

Individuals younger than 18 years old;, those with a history of ischemic heart disease polycystic kidney disease, malignancy or chronic liver disease;, those with a history of infection within the previous 4 weeks;, and those fitted with a pacemaker or implanted pump, or with an amputation were excluded from the study. The study protocol was approved by the Human Subjects Institutional Review Board of the Inje University Haeundae Paik Hospital (2012–057), and all participants signed the requisite informed consent forms.

2.2. Laboratory measurements

Fasting blood samples were obtained by venipuncture from all patients and controls using standard containers. Hemoglobin, serum albumin, calcium, phosphorus, urea nitrogen, creatinine, uric acid, CK-MB, cardiac troponin-I, and serum sodium were measured by the central laboratory of the Inje University Haeundae Paik Hospital.

NT-proBNP was measured using an electrochemiluminescence immunoassay kit (Roche) according to the manufacturer's specifications. Plasma copeptin, pro-adrenomedullin, and myeloperoxidase were measured using enzyme-linked immunosorbent assay kits, purchased from Phoenix Pharmaceuticals, Cusabio Biotech, and R&D systems, respectively, according to the manufacturers' specifications.

2.3. Assessment of body composition

Using the BCM, we determined body composition prior to dialysis in HD patients, and with a dry abdomen in PD patients, after the patient had rested in a supine position for at least 5 min, Electrodes were placed on the wrist of the arm without an arteriovenous fistula and on the ipsilateral ankle and connected to the BCM device. The BCM measures body resistance and reactance to electrical currents of 50 discrete frequencies, ranging from 5 to 1000 kHz. On the basis of a fluid model using these resistances, we calculated the amount of extracellular water, intracellular water, total body water, and volume overload. Relative hydration status (ΔHS) was defined in terms of the hydration-to-extracellular water ratio with a cutoff of 15%, and hyperhydrated status was defined as ΔHS > 15%.

2.4. Transthoracic echocardiography assessments

For echocardiographic measurements, we used a General Electric Vivid E9 echocardiography device. Standard parasternal and apical three- and four-chamber views were obtained and two investigators performed and analyzed the echocardiographic data. Calculations of left ventricular end-diastolic, -systolic volume, and ejection fraction were performed by using the Simpson method.

2.5. Statistical analysis

The Mann–Whitney *U* test for continuous variables was used and Bonferroni's method was used for adjustment for multiple

comparisons. Spearman coefficient for regression analysis was used for statistical analysis of the data, which are expressed as median (interquartile range). Correlations between NT-proBNP, myeloperoxidase, copeptin, and pro-adrenomedullin and other laboratory factors were analyzed using univariate regression analysis followed by multivariate regression analysis. A *P*-value $\leq .05$ was considered significant.

3. Results

3.1. Characteristics of the study groups

Data relating to participant characteristics are summarized in Table 1. As expected, patients in the HD and PD groups had elevated blood pressure, anemia, hypoalbuminemia, and high-sensitivity C-reactive protein (hs-CRP) concentrations. No significant difference was detected in the body mass index or serum sodium concentration between individuals in the dialysis and control groups.

3.2. NT-proBNP, myeloperoxidase, copeptin, and pro-adrenomedullin data

Data for plasma NT-proBNP, copeptin, myeloperoxidase, and pro-adrenomedullin concentrations in the four study groups are summarized in Table 2. We found that plasma NT-proBNP concentration in the pre-dialysis (1078.2 ± 746.7 pg/dL), HD (2931.3 ± 793.6 pg/dL), and PD (3560.9 ± 857.9 pg/dL) groups was significantly higher than that in the control group (31.5 ± 4.3 pg/dL). Similarly, plasma pro-adrenomedullin concentration in the pre-dialysis (19.54 ± 3.49 pmol/L), HD (27.26 ± 5.71 pmol/L), and PD (30.39 ± 5.91 pmol/L) groups was significantly higher than that in the control group (8.39 ± 1.43 pmol/L). In contrast, there were no significant differences in myeloperoxidase and copeptin concentrations among the study groups.

3.3. Body composition monitoring data

Body composition data for the study participants are summarized in Table 3. We detected no significant differences in total body water, extracellular water, or intracellular water among the four groups. In the control subjects and pre-dialysis patients, mean amount of volume overload were 0.6 ± 0.2 L and 1.9 ± 1.0 L, respectively, whereas in the HD and PD patients, levels were significantly higher at 2.8 ± 0.6 L and 3.0 ± 0.5 L, respectively ($P < .001$). Moreover, we found that the hyperhydrated status was more pronounced in the HD and PD patients compared with the pre-dialysis patients (35% vs 55% vs 20%, respectively, $P = .001$).

3.4. Transthoracic echocardiography data

Echocardiographic data for the study participants are summarized in Table 4. Compared with the control group, left ventricular (LV) mass, LV mass index, left atrial diameter, and E/E′ ratio were significantly higher in pre-dialysis, HD, and PD patients, whereas in contrast, ejection fraction was significantly lower.

3.5. Correlations between relative hydration status and biomarkers for volume status or cardiac markers

We detected significant associations between relative hydration status and higher NT-proBNP or pro-adrenomedullin levels in HD and PD patients compared with those in the control and pre-dialysis groups ($r = 0.454$ [$P < .001$] and $r = 0.505$ [$P < .001$], respectively), although not myeloperoxidase and copeptin levels

Table 1

Baseline characteristics of predialysis, hemodialysis, and peritoneal dialysis patients, and healthy controls.

	Control	Predialysis	Hemodialysis	Peritoneal dialysis
Age, years	31 (26, 35)	53 (46, 60)	56 (46, 69)	53 (47, 63)
Gender (male: female)	10: 10	11: 9	11: 9	11: 9
Cause of CKD/ESRD				
Diabetes mellitus	NA	9 (45)	8 (40)	10 (50)
Hypertension	NA	5 (25)	7 (35)	8 (40)
Chronic GN	NA	5 (25)	2 (10)	1 (5)
Others	NA	1 (5)	3 (15)	1 (5)
Systolic blood pressure (mm Hg)	110 (100, 120)	129 (116, 140)[b]	145 (130, 160)[a]	130 (120, 158)[a]
Diastolic blood pressure (mm Hg)	80 (60, 80)	80 (79, 88)[b]	85 (80, 90)[a]	85 (80, 90)[a]
Body weight (kg)	64 (51, 82)	66 (56, 77)[f]	65 (53, 78)[f]	70 (61, 78)[a,d]
Body mass index (kg/m^2)	22.9 (20.2, 27.1)	24.1 (21.0, 27.3)	23.3 (21.5, 27.6)	25.5 (22.2, 28.0)
Hemoglobin (g/dL)	14.3 (13.0, 15.8)	11.0 (10.1, 12.6)[a,d,f]	10.3 (9.6, 10.9)[a]	10.2 (9.7, 11.0)[a]
Serum albumin (g/dL)	4.5 (4.4, 4.7)	3.9 (3.5, 4.2)[a,e]	3.7 (3.4, 3.8)[a,f]	3.3 (3.0, 3.8)[a,d]
Serum urea nitrogen (mg/dL)	12.1 (9.2, 13.9)	52.6 (30.7, 63.1)[a,c,e]	77.8 (60.2, 82.3)[a]	54.3 (43.2, 69.7)[a]
Serum creatinine (mg/dL)	0.9 (0.8, 1.0)	3.6 (2.4, 4.9) [a,c,e]	10.3 (8.9, 12.4) [a]	9.7 (6.2, 14.9) [a]
hs-CRP (mg/dL)	0.03 (0.02, 0.04)	0.15 (0.09, 0.38)[a]	0.17 (0.07, 0.48) [a]	0.16 (0.08, 0.31) [a]
CK-MB (ng/mL)	NA	1.4 (1.1, 1.6)	2.0 (1.1, 3.1)	2.2 (1.4, 3.6)
Cardiac troponin-I (ng/mL)	NA	0.02 (0.01, 0.03)	0.02 (0.01, 0.04)	0.02 (0.01, 0.05)
Uric acid (mg/dL)	NA	7.9 (7.2, 8.9)[a]	7.3 (6.6, 8.1)[a]	6.7 (6.4, 8.2)[a]
Serum Na (meq/L)	139 (137, 141)	140 (139, 141)	138 (136, 140)	138 (136, 141)

Values are expressed as median (interquartile range).

CKD/ESRD = chronic kidney disease/end-stage renal disease, GN = glomerulonephritis, hs-CRP = high-sensitivity C-reactive protein.

[a]$P < .001$, [b]$P < .05$ versus control group.

[c]$P < .001$, [d]$P < .05$ versus hemodialysis group.

[e]$P < .001$, [f]$P < .05$ versus peritoneal dialysis group.

Table 2

Plasma NT-proBNP, copeptin, myeloperoxidase, and pro-adrenomedullin concentrations in predialysis, hemodialysis, and peritoneal dialysis patients, and healthy controls.

	Control	Predialysis	Hemodialysis	Peritoneal dialysis
NT-proBNP (pg/dL)	30.3 (17.9, 39.5)	278.2 (102.3, 486.9)[a,c,e]	3511.5 (1060.0, 32899.5)[a,e]	6510 (734.8, 38756.5)[a,c]
Copeptin (ng/mL)	0.40 (0.29, 0.49)	0.29 (0.19, 0.48)	0.40 (0.33, 0.45)	0.35 (0.26, 0.47)
Myeloperoxidase (ng/mL)	0.96 (0.41, 3.73)	0.58 (0.46, 0.79)	0.39 (0.32, 0.53)	0.55 (0.45, 0.91)
Proadrenomedullin (pmol/L)	8.64 (2.44, 11.31)	15.77 (8.93, 26.51)[a,c,e]	20.91 (12.43, 35.59)[a,f]	21.75 (8.90, 51.94)[a,d]

Values are expressed as median (interquartile range).
NT-proBNP = N-terminal pro-B-type natriuretic peptide.
[a]$P < .001$, [b]$P < .05$ versus control group.
[c]$P < .001$, [d]$P < .05$ versus hemodialysis group.
[e]$P < .001$, [f]$P < .05$ versus peritoneal dialysis group.

(Fig. 1). Furthermore, these were significantly associated with cardiac markers (LV mass, LV mass index, ejection fraction, and left atrial diameter) in the HD and PD patients compared with those in the control and pre-dialysis groups ($r = 0.529$ [$P < .001$]; $r = -0.302$ [$P < .001$]; $r = 0.578$ [$P < .001$], respectively), but not with E/E' ratio (Fig. 2).

4. Discussion

Volume overload is considered a major cause of hypertension, heart failure, and cardiovascular-related mortality in patients with ESRD on maintenance dialysis.[23] Therefore, the early diagnosis and treatment of volume overload can lead to an improvement in the survival rate of dialysis patients. In clinical practice, however, determination of the volume status of these patients is typically based solely on clinical observations, such as blood pressure, weight gain, peripheral edema, and detection of cardiomegaly or pulmonary edema in chest X-rays. Nevertheless, these findings do not always provide an accurate assessment of volume status.[24] Accordingly a range of alternate methods are increasingly being adopted in an effort to provide more precise determinations of body fluid volume. Among these, bioimpedance techniques can estimate extracellular volume, intracellular volume, and total body water, whereas biochemical markers (such as atrial natriuretic and brain natriuretic peptides) can provide information concerning the intravascular filling state.[25] In the present study, we used the BCM, a non-invasive, multifrequency bioimpedance device, to evaluate the volume status in healthy individuals and pre-dialysis and dialysis patients, with a particular focus on the association between volume overload and the risk of cardiovascular disease.[26] On the basis of our BCM and echocardiography findings, we demonstrate associations among novel biomarkers, volume status, and cardiovascular risk in dialysis patients.

The BCM has been used as the gold standard for measurement of volume status,[27] and recent studies have shown that volume overload, as detected by the BCM, can serve as an independent predictor of mortality.[26,28] However, it remains to be determined whether a range of different volume markers can be used to accurately determine volume status in ESRD patients.

Previously, NT-proBNP has been employed as a useful predictor of mortality in ESRD patients,[29–31] and NT-proBNP levels have proved effective in estimating the prognosis of chronic heart failure patients with left ventricular mass and fluid volume overload.[32] In the present study, we found that plasma NT-proBNP concentrations in the dialysis groups were significantly higher than those in the control and pre-dialysis groups, and that elevated NT-proBNP levels were associated with volume

Table 3

Body composition monitor data of pre-dialysis, hemodialysis, and peritoneal dialysis patients, and healthy controls.

	Control	Predialysis	Hemodialysis	Peritoneal dialysis
TBW (L)	35.8 (26.4, 39.7)	35.5 (29.6, 41.5)	31.0 (28.5, 39.5)	35.6 (28.7, 38.8)
TBW/BW (L/kg)	0.49 (0.47, 0.56)	0.55 (0.47, 0.57)	0.52 (0.49, 0.55)	0.49 (0.44, 0.56)
ECW (L)	14.9 (11.8, 18.0)	16.5 (14.9, 18.2)	15.2 (13.1, 20.2)	17.5 (14.6, 19.6)
ECW/BW (L/kg)	0.22 (0.21, 0.24)	0.25 (0.23, 0.26)	0.25 (0.22, 0.27)	0.25 (0.22, 0.26)
ICW (L)	19.8 (14.7, 21.9)	17.6 (15.5, 21.8)[f]	16.6 (14.3, 19.8)	17.3 (13.7, 19.8)
ICW/BW (L/kg)	0.27 (0.26, 0.32)	0.29 (0.23, 0.32)	0.26 (0.23, 0.29)	0.25 (0.21, 0.26)
Volume overload (L)	0.6 (0.2, 1.1)	0.8 (0.03, 2.1)[b,c,e]	2.1 (1.0, 5.1)[a]	3.0 (1.3, 4.5)[a]
Volume overload (mL/kg)	11.0 (0, 16.0)	12.5 (0.5, 34.0)[b,c,e]	29.5 (4.0, 68.0)[a]	48.0 (17.8, 71.8)[a]
ECW/ICW	0.80 (0.75, 0.85)	0.85 (0.78, 0.94)[c,e]	0.95 (0.89, 1.09)[a]	1.06 (0.90, 1.13)[a]
ECW/TBW	0.45 (0.43, 0.46)	0.46 (0.44, 0.49)[f]	0.49 (0.47, 0.52)[a]	0.52 (0.47, 0.53)[a]
Relative hydration status (%)	5.1 (1.0, 7.4)	5.3 (0.04, 13.2)[a,c,e]	12.7 (7.2, 23.6)[a]	17.7 (8.3, 24.2)[a]
Lean tissue index (kg/m^2)	14.0 (12.5, 145)	13.8 (12.2, 16.4)	12.8 (10.9, 15.0)	11.9 (10.1, 13.6)
Fat tissue index (kg/m^2)	9.9 (6.8, 12.7)	7.9 (6.8, 11.0)	9.4 (7.8, 13.1)	12.1 (7.8, 15.2)

Values are expressed as median (interquartile range).
Relative hydration status = hydration status/extracellular water (%).
BW = body weight, ECW = extracellular water, ICW = intracellular water, TBW = total body water.
[a]$P < .001$, [b]$P < .05$ versus control group.
[c]$P < .001$, [d]$P < .05$ versus hemodialysis group.
[e]$P < .001$, [f]$P < .05$ versus peritoneal dialysis group.

Table 4

Echocardiographic data of pre-dialysis, hemodialysis, and peritoneal dialysis patients, and healthy controls.

	Control	Predialysis	Hemodialysis	Peritoneal dialysis
LV mass	102.5 (91.0, 127.0)	155.0 (119.5, 231.3)[a,c,e]	248.0 (174.0, 280.3)[a]	231.5 (192.3, 271.0)[a]
LVMI (g/m^2)	61.9 (57.3, 74.3)	88.1 (73.6, 117.1)[a,c,e]	132.8 (102.4, 175.1)[a]	137.9 (104.5, 148.9)[a]
LVIDd	4.6 (4.4, 4.8)	4.9 (4.6, 5.4)[b]	5.3 (4.8, 5.9)[a]	5.2 (4.8, 5.4)[a]
LVIDs	3.0 (2.9, 3.1)	3.1 (3.0, 3.5)	3.7 (3.1, 4.1)[a]	3.4 (3.2, 3.9)[a]
LVEF (%)	66.0 (64.8, 66.3)	65.0 (61.3, 66.0)[b]	60.0 (57.3, 65.0)[a]	60.0 (57.3, 63.8)[b]
LA diameter	3.4 (3.0, 3.7)	3.6 (3.3, 4.0)[b,d,f]	4.3 (3.8, 4.9)[a]	4.2 (3.8, 4.6)[a]
EA ratio	1.6 (1.4, 2.0)	0.8 (0.7, 0.9)[a]	0.8 (0.7, 1.2)[a]	0.8 (0.5, 0.9)[a]
E/E' ratio	5.8 (5.3, 6.2)	9.3 (8.0, 12.7)[b]	14.3 (11.0, 21.2)[a]	10.8 (7.4, 14.6)[a]

Values are expressed as median (interquartile range).

LA = left atrium, LVEF = left ventricular ejection, fraction, LVID = left ventricular internal dimension, LVMI = left ventricular mass index.

[a]$P < .001$, [b]$P < .05$ versus control group.

[c]$P < .001$, [d]$P < .05$ versus hemodialysis group.

[e]$P < .001$, [f]$P < .05$ versus peritoneal dialysis group.

overloading. Adrenomedullin is a potent vasodilator with inotropic and natriuretic properties and the plasma concentrations of this compound are influenced by body fluid volume status.[33] Previous studies have shown that plasma levels of adrenomedullin are associated with systemic blood volume and cardiovascular disease.[33–36] In the present study, instead of measuring adrenomedullin per se, we measured mid-regional pro-adrenomedullin, as adrenomedullin itself has a short half-life and is unstable in plasma at room temperature. We also showed that plasma pro-adrenomedullin concentrations in the dialysis group patients were significantly higher than those in the control and pre-dialysis groups, and found that elevated pro-adrenomedullin levels were associated with volume overloading.

Levels of myeloperoxidase in plasma are associated with an increased susceptibility to ESRD or chronic heart failure via an elevation in oxidative stress and endothelial dysfunction.[18] Plasma myeloperoxidase levels not only have an independent prognostic cardiovascular value in heart failure patients but also have significant independent prognostic and risk stratification value in ESRD patients.[37] Although an association between the plasma levels of copeptin and cardiovascular events and mortality has been previously reported in a study examining a cohort of the 4D study (German Diabetes Dialysis Study),[38] the findings of the present study indicate that whereas plasma NT-proBNP and pro-adrenomedullin concentrations were associated with volume overload and cardiac dysfunction, myeloperoxidase and copeptin showed no similar associations.

ESRD patients are known to have a high burden of conventional risk factors that are closely related to atherosclerosis, left ventricular dilatation with hypertrophy, systolic dysfunction, and high left ventricular filling pressure. Furthermore, ESRD is associated with left ventricular fibrosis, stiffness, and relaxation abnormality. The most important variable in echocardiography is the *E*/*E*′ ratio (left ventricular filling pressure/left ventricular relaxation) and *E*/*E*′ values serve as the most powerful prognostic indicators in both systolic and diastolic heart failure, myocardial infarction, cardiomyopathy, and left ventricular hypertrophy.[39,40] In this regard, we found that left ventricular mass index, left ventricular dimension and ejection fraction, left atrial diameter, and *E*/*E*′ ratio were related

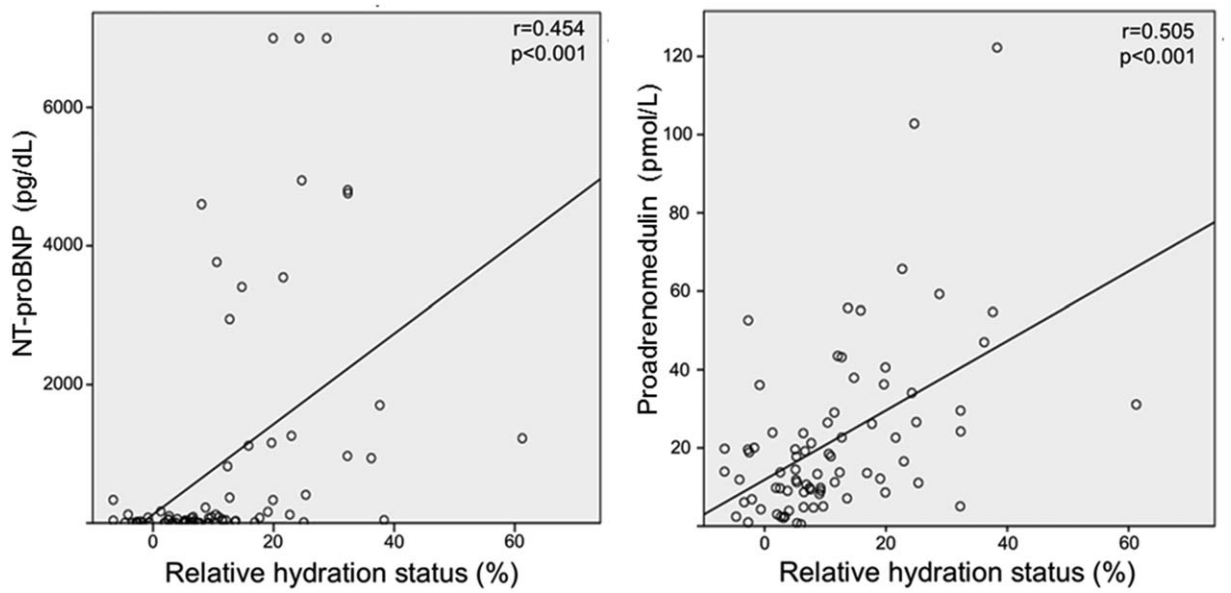

Figure 1. Correlations between plasma NT-proBNP or pro-adrenomedullin concentrations and the relative hydration status of individuals in the study population. The *r* value represents the non-parametric Spearman correlation coefficient.

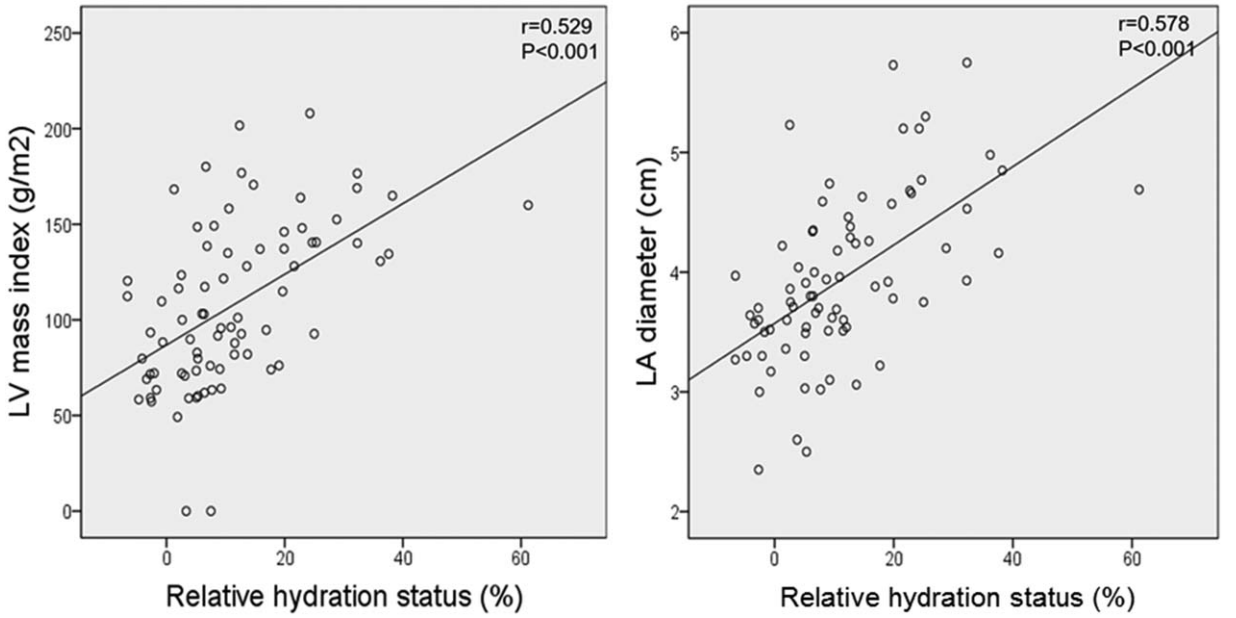

Figure 2. Correlations between the relative hydration status and cardiac markers of individuals in the study population. The *r* value represents the non-parametric Spearman correlation coefficient.

to hydration status based on BCM and that hyperhydrated status was directly related to the concentrations of NT-proBNP and pro-adrenomedullin.

There are several limitations to this study that should be noted. Most importantly, this was a single-center, cross-sectional study with a small study population, and as such, it is not possible to conclusively establish causal relationships. Moreover, the findings of the study do not necessarily indicate that better volume control could reduce cardiovascular-related mortality. However, we have demonstrated the relationships between body fluid status and volume markers in dialysis patients and the utility of biomarkers associated with volume status. Finally, we did not collect the data of 20 HD patients on interdialytic weight gain.

In conclusion, we analyzed that elevated levels of NT-proBNP and pro-adrenomedullin are associated with volume overloading in dialysis patients, whereas myeloperoxidase and copeptin levels are probably not. In conclusion, we infer that elevated levels of NT-proBNP and pro-adrenomedullin are associated with volume overload in dialysis patients, whereas myeloperoxidase and copeptin levels do not appear to correlate with volume status. Accordingly, we might be able to make early predictions regarding the volume overload status of dialysis patients based on the detection of increased plasma concentrations of NT-proBNP and pro-adrenomedullin, thereby potentially reducing cardiovascular-related mortality by enabling appropriate early volume control.

Author contributions

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