

# Total body water/fat-free mass ratio as a valuable predictive parameter for mortality in maintenance hemodialysis patients

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# Abstract

Hydration of fat-free mass (FFM), defined as the ratio of total body water (TBW) to FFM (TBW/FFM), is stable at 0.739 in adult mammals. However, an increase in the TBW/FFM ratio is common in hemodialysis (HD) patients. This study aimed to evaluate the determinants of TBW/FFM and investigate its predictive value for the prognosis of all-cause mortality in HD patients.

We enrolled patients undergoing maintenance HD between July 2020 and May 2021. All patients were prospectively followed until death, HD dropout, or until the end of the study (November 1, 2021). A forward stepwise multivariable linear regression analyses was performed to test the independent relationship between TBW/FMM and other clinical variables. Receiver operating characteristic (ROC) analysis was used to discriminate the TBW/FFM with respect to 180-day mortality.

Of the 106 patients, 42 had elevated TBW/FFM levels. Multiple linear regression analysis revealed that the TBW/FFM ratio was significantly associated with extracellular water (ECW)/TBW (standardized regression coefficient [ $\beta$  = 1.131, *P* < .001], phase angle (PhA) [ $\beta$  = 0.453, *P* < .001], and sex ( $\beta$  = 0.440, *P* < .001). We calculated the ROC curve (AUC) of TBW/FFM, ECW, ECW/TBW, and intracellular water (ICW) to compare the discriminatory capacities of these parameters in predicting 180-day mortality. The AUC for TBW/FFM (AUC = 0.849; 95% CI, 0.745–0.953) exhibited better discriminatory potential than ECW (AUC = 0.562; 0.410–0.714), although it had a similar predictive potential as the ECW/TBW ratio (AUC = 0.831; 0.731–0.932). High TBW/FFM can be used as a valuable prognostic index for predicting all-cause mortality in patients on HD.

**Abbreviations:** BCM = body cell mass, BIA = bioelectrical impedance analyzer, BNP = brain natriuretic peptide, DM = diabetes mellitus, ECW = extracellular water, FFM = fat-free mass, FM = fat mass, HD = hemodialysis, PhA = phase angle, ROC = receiver operating characteristic, SMM = skeletal muscle mass, SMI = skeletal muscle mass index, TBW = total body water.

Keywords: bioelectrical impedance analyzer, fat-free mass, total body water, hemodialysis, overhydration, mortality

# 1. Introduction

Hemodialysis (HD) is the primary treatment for end-stage renal disease. Although new dialysis techniques allow higher fluid volumes to be removed, overhydration becomes a problem in patients undergoing maintenance HD.<sup>[1]</sup> Fluid overload is independently associated with cardiovascular and all-cause mortality in such patients.<sup>[2,3]</sup> Strict control of fluid intake and maintenance of a normotensive state improves the survival rate of HD patients.<sup>[4,5]</sup>

Bioelectrical impedance analyzer (BIA) has been recommended for the assessment of water distribution and nutritional status by body composition assessment in patients requiring maintenance HD.<sup>[6,7]</sup> BIA indirectly identifies body composition using the different electrical conductivities of different organs and tissues.<sup>[8]</sup> It assumes that the human body is composed of fat mass (FM; high electrical impedance) and fat-free mass (FFM;

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low electrical impedance).<sup>[9]</sup> FFM has a complex composition, including muscle mass, bone mass, electrolytes, and water, which have a low electrical impedance and cause the current to flow mainly from the FMM.<sup>[9]</sup> Therefore, FFM has a higher conductivity than that of FM. Hydration of FFM, defined as the ratio of total body water (TBW) to FFM (TBW/FFM), is stable at 0.739 in adult mammals; however, FFM hydration may be higher in neonates, obese persons, and elderly persons.<sup>[10]</sup> Besides, even patients with end-stage renal disease who are on HD can accumulate large volumes of fluid between dialysis sessions, potentially increasing the level of hydration of FFM.<sup>[10,11]</sup>

An increase in the TBW/FFM ratio is common in HD patients<sup>[10,11]</sup>; however, the value of the TBW/FFM ratio in HD patients remains to be fully illustrated. Hence, this study aimed to evaluate the determinants of TBW/FFM and investigate its predictive value for the prognosis of all-cause mortality in HD patients.

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This study was approved by the institutional review board for human research at the Shibei Hospital of Jing'an District, Shanghai (no. 20200320-06).

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# 2. Methods

We conducted a prospective cohort study of patients who required maintenance HD. This study was approved by the Institutional Review Board for Human Research at Shibei Hospital of Jing'an District, Shanghai (no. 20200320-06), and all participants provided written informed consent prior to study enrollment. We enrolled patients on maintenance HD from the dialysis centers of Shibei Hospital between July 2020 and May 2021. All patients underwent regular dialysis for 3.5-4 hours, thrice-weekly. Our study included 106 patients based on the following inclusion criteria: (1) age  $\geq 18$  years. (2) All participants had been on HD for 3 months. Exclusion criteria: (1) Patient with a pacemaker. (2) Patients with amputation and limb defects. All patients were prospectively followed until death, HD dropout, or until the end of the study (November 1, 2021). The primary outcome in our study was all-cause mortality.

# 2.1. Data Collection

We collected the baseline clinical data (age, sex, and comorbidities: diabetes, sarcopenia, or heart failure). White blood cell count, platelet count, and baseline biochemical parameters, including total lipid profile, hemoglobin, C-reactive protein, serum calcium, serum phosphorus, albumin, brain natriuretic peptide (BNP), and troponin-I, were analyzed on the morning of the day of enrollment. The efficiency of dialysis was assessed based on the delivered dose of dialysis spKt/V using the natural logarithm formula of Daugirdas, and the urea reduction ratio (URR) was calculated using predialysis urea nitrogen and postdialysis urea nitrogen. All laboratory tests were performed prior to dialysis.

# 2.2. Body composition assessment

Body composition was measured using a BIA (InBody S10; Biospace, Seoul, South Korea) with 6 different frequencies (1, 5, 50, 250, 500, and 1000 kHz). Weight and height were measured before BIA. We performed BIA within 30 minutes of dialysis with patients in the supine position. The parameters assessed by BIA were intracellular water (ICW), extracellular water (ECW), protein, minerals, fat-free mass (FFM), fat mass (FM), skeletal muscle mass (SMM), body cell mass (BCM), and phase angle (PhA). The ICW, ECW, FFM, BCM, and FM were calculated using multiple regression equations.<sup>[12,13]</sup> Using reactance (Xc) and resistance (R) obtained from BIA at 1-1000 kHz, the phase angle was calculated using the following equation at 50 kHz: phase angle (degrees) = arctan (Xc/R) ×  $(180/\pi)$ .<sup>[14]</sup> BMI (kg/m<sup>2</sup>) = weight  $(kg)/height^2$  (m). SMI = total skeletal muscle mass (kg)/weight<sup>2</sup> (kg).<sup>[15]</sup> Protein = BCM – ICW; minerals = FFM – (TBW + protein); TBW = ICW + ECW.<sup>[10]</sup> All parameters were calculated automatically by the BIA software.

#### 2.3. Statistical Analysis

Univariate analysis was performed with the Student t-test or Mann–Whitney U test to evaluate the differences in continuous variables and the Chi-square test for those in proportion. Spearman correlation analysis was performed to estimate the correlation between TBW/FFM and the other parameters derived from BIA. A forward stepwise multivariable linear regression analyses was performed to test the independent relationship between TBW/FMM and other clinical variables. Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test, and receiver operating characteristic (ROC) analysis was used to discriminate the TBW/FFM with respect to 180-day mortality. All tests were 2-sided and P values < 0.05 were considered statistically significant. Data were analyzed using SPSS software, version 20.0, for Microsoft Windows (SPSS, Inc., Chicago, IL).

# 3. Results

### 3.1. Characteristics of the patients

A total of 106 patients were included in our study, no one dropped out of whom 66 were men and 40 were women, with a median age of 65 years (interquartile range [IQR] 32–87). Overall, the 180-day mortality rate was 5.7% (6 of 107). The patients were classified according to the TBW/FFM level (TBW/ FFM  $\leq$  73.9 and TBW/FFM > 73.9). Of 106 patients, 42 had elevated TBW/FFM levels. Univariate analysis revealed that male patients (*P* < .001) had higher TBW/FFM value. The prevalence of diabetes mellitus (DM) (*P* = .015), heart failure (*P* = .031), and mortality rate (*P* = .031) were significantly higher in the group with higher TBW/FFM. In contrast, there were no significant differences in age or incidence of sarcopenia between the groups (Table 1).

# 3.2. Association between TBW/FFM and laboratory parameters

When the laboratory parameters were compared between the 2 groups, albumin (P = .017), URR (P = .003), spKt/v (P = .038), and phosphorus (P = .010) levels were significantly lower in the group with TBW/FFM  $\leq 73.9$ . In contrast, BNP (P = .005) and troponin-I (P = .003) were significantly higher in the TBW/FFM group with TBW/FFM  $\leq 73.9$ . Moreover, other laboratory parameters, such as white blood cell count, hemoglobin, platelet count, C-reactive protein, serum calcium, and lipid profiles, did not show any significant differences between the groups (Table 1).

# 3.3. Correlation analysis between TBW/FFM and BIAassessed parameters

Spearman correlation analysis showed that TBW/FFM was correlated with ECW/TBW (R = 0.526, P < .001) and PhA (r = -0.400, P < .001) in both men and women. ECW (r = -0.341, P = .031) was correlated with TBW/FFM in women (Table 2). We performed multiple linear regression analysis using variables that correlated with TBW/FMM (P < .05) in the univariate analysis: BNP, sex, troponin-I, phase angle, ECW/TBW, ECW, heart failure, and diabetes mellitus. After adjustment by BNP, troponin-I, ECW, heart failure, and diabetes mellitus, the TBW/FFM ratio was significantly associated with ECW/TBW (standardized regression coefficient [ $\beta = 1.121$ , P < .001], PhA [ $\beta = 0.444$ , P < .001], and sex [ $\beta = -0.435$ , P < .001]) (Table 3).

#### 3.4. K-M curve

A log-rank test further confirmed that TBW/FFM was associated with higher 180-day mortality (95% CI, 163.111–177.776; P = .025) (Fig. 1).

# 3.5. ROC analysis

We calculated the areas under the ROC curve (AUC) of TBW/ FFM, ECW/TBW, ICW, and ECW to compare the discriminatory capacities of these parameters in predicting 180-day mortality. The AUC for TBW/FFM (AUC = 0.849; 95% CI, 0.745–0.953) exhibited a better discriminatory potential than ECW (0.562; 0.410–0.714), although it had a similar predictive potential as the ECW/TBW ratio (0.831; 0.731–0.932) (Fig. 2).

#### Table 1

Demographic and laboratory data according to tertiles of total body water/fat-free mass ratio in hemodialysis patients.

Characteristic	Normal	Elevated	<i>P</i> value
Age, yr	64 (33–84)	66 (32–87)	0.077
Male/female	34/30	32/10	0.024
White blood cell, 10 <sup>9</sup> /L	5.51 (2.18–13.70)	5.69 (3.15–14.30)	0.869
Hemoglobin, g/L	$107.85 \pm 10.63$	$105.92 \pm 16.90$	0.775
Platelet, 10 <sup>9</sup> /L	$163.34 \pm 54.00$	$148.65 \pm 50.52$	0.056
Serum calcium, mmol/L	2.33 (1.97-2.91)	2.28 (1.93-3.30)	0.619
Serum phosphorus, mmol/L	1.58 (0.18-3.07)	1.35 (0.06–2,85)	0.010
Serum albumin, g/L	$36.52 \pm 3.03$	$34.68 \pm 4.27$	0.017
Troponin-I, ng/mL	0.010 (0.00-0.07)	0.025 (0.00-1.17)	0.000
spKt/v	$1.46 \pm 0.24$	$1.31 \pm 0.25$	0.038
URR, %	70 (55-80.6)	63 (51–79)	0.003
HDL, mmol/L	0.86 (0.55-1.68)	0.96 (0.25-1.46)	0.545
LDL, mmol/L	$2.12 \pm 0.67$	$1.89 \pm 0.90$	0.393
Cholesterol, mmol/L	3.64 (2.41–6.45)	3.56 (2.16-6.97)	0.335
Triglyceride, mmol/L	1.70 (0.66–7.27)	1.58 (0.22-5.80)	0.356
C-react P, mg/L	1.70 (0.80–184.00)	2.30 (0.80–153.00)	0.081
BNP, pg/L	99.00 (8.29–1986.00)	223.80 (10.90-5000.00)	0.003
Diabetes melitus, n (%)	19 (29.69%)	23 (54.76%)	0.015
Heart failure, n (%)	0 (0)	11 (15.07%)	0.031
Sarcopenia, n (%)	28 (45.16%)	22 (52.38%)	0.550
nonsurvivors, n (%)	1 (1.56%)	5 (7.58%)	0.031

Data are presented as means ± SD or median (minimum and maximum) and categorical variable is presented as no, (%).

BNP = Brain natriuretic peptide, HDL = High density lipoprotein, LDL = Low density lipoprotein, Single pool Kt/v = spKt/v, URR = urea reduction ratio.

# Table 2

Spearman correlation between total body water/fat-free mass ratio and variables from bioelectrical impedance analyzer in hemodialysis patients.

Variable	Man	P value	Woman	P value
ECW, L	0.190	0.127	0.341	0.031
ICW, L	-0.211	0.089	-0.071	0.662
ECW/TBW, %	0.826	0.000	0.530	0.000
Phase angle (°)	-0.678	0.000	-0.390	0.013
BMI, kg/m <sup>2</sup>	-0.193	0.121	0.289	0.071
Fat mass, kg	-0.222	0.073	0.282	0.078
Protein, kg	-0.189	0.128	0.125	0.441
Mineral, kg	-0.187	0.133	-0.149	0.359
BCM, kg	0.195	0.045	-0.014	0.930
FFM, kg	-0.025	0.843	-0.203	0.209
SMI, kg/m <sup>2</sup>	0.144	0.249	-0.306	0.055

ICW = intracellular water, BCM = body cell mass, BMI = body mass index, ECW = extracellular water, FFM = fat free mass, SMI = skeletal muscle mass index.

# 4. Discussion

The main finding of our study was that higher TBW/FFM was accompanied with higher BNP, troponin I, and ECW/TBW. In contrast, albumin, spKt/v, URR, and PhA levels were lower in patients with higher TBW/FFM. A higher TBW/FFM ratio was associated with diabetes and heart failure. Multivariate regression analysis showed that TBW/FFM, PhA, and sex were independent predictors of the TBW/FFM ratio. A higher TBW/FFM ratio was associated with all-cause mortality in the K-M curve. TBW/FFM could be used as a valuable, objective predictive parameter for mortality in patients undergoing HD.

Clinically, volume status evaluations in HD patients are usually based on clinical signs, biochemical parameters, and inferior vena cave diameter on ultrasonography; however, they do not accurate and depend on the physician's experience or invasiveness. BIA has gained popularity in recent years and has been proposed as a noninvasive and reproducible tool for the assessment of volume status in HD patients. The TBW/FFM ratio, automatically calculated by BIA device. Large volumes of fluid in HD patients, potentially increasing the level of hydration of

# Table 3

Multivariable linear regression analyses to test independent relationship between total body water/fat-free mass ratio and other clinical variables.

Variable	$\beta$ Coefficient	95% CI	P value
Model 1 (R <sup>2</sup> = 0.658)			
ECW/TBW	0.648	15.290-24.274	0.000
Model 2 (R <sup>2</sup> = 0.808)			
ECW/TBW	0.727	18.284-25.472	0.000
Gender	-0.474	-0.638 to-0.382	0.000
Model 3 (R <sup>2</sup> = 0.830)			
ECW/TBW	1.121	25.960-41.431	0.000
Gender	-0.435	(-0.592) to (-0.344)	0.000
Phase angle (°)	0.444	0.076-0.294	0.000

ECW = extracellular water, TBW = total body water.

FFM. Hence, the TBW/FFM ratio may use as an index to evaluate the volume status of patients undergoing HD.<sup>[10,11]</sup> In our study, we found that 39.6% of HD patients had an elevated TBW/FFM ratio, and men had higher TBW/FFM levels than women, suggesting that men may have worse fluid control than women in our center. Overhydration has also been linked to heart failure.<sup>[16,17]</sup> In our study, all patients with heart failure had high TBW/FFM levels. Given the increasing prevalence of heart failure in dialysis patients, it is not surprising that higher TBW/ FFM was associated with higher BNP and troponin-I levels in our study. Furthermore, our study found that patients with a higher TBW/FFM ratio were more likely to be diabetic. Previous studies have found that diabetic patients undergoing dialysis have a greater fluid overload than nondiabetic patients.[18,19] This may be because DM patients with poor diabetic control have increased thirst, which causes fluid overload.<sup>[20]</sup>

Malnutrition is a common complication that can predict mortality in patients undergoing HD.<sup>[21,22]</sup> In our study, a high TBW/FFM ratio was associated with lower serum albumin and PhA values, both of which are indicators of malnutrition in HD patients<sup>[23,24]</sup> suggesting that TBW/FFM indicates hydration as well as malnutrition in these patients. This may be because malnutrition can reduce ICW.<sup>[25]</sup> Meanwhile,



Figure 1. Kaplan-Meier survival curves of 106 hemodialysis patients stratified according to TBW/FFM, The *P* values were derived using a log-rank test.



Figure 2. The receiver operating characteristic (ROC) curves constructed for 180-day mortality outcome prediction using ECW/TBW, TBW/FFM, ECW, ICW in 106 hemodialysis patients.

malnutrition may also cause tissue overhydration,<sup>[26]</sup> a previous study showed that in dialysis patients, hypoalbuminemia is associated with measurable excess body water, and that excess fluid is not equally in the intravascular space but lies in the extravascular space as hypoalbuminemia reduces the osmotic pressure.<sup>[26]</sup>

Multivariate regression analysis revealed that elevated ECW/ TBW ratio was the most important determinant of a higher TBW/FFM ratio. This is consistent with a previous study that showed that ECW/TBW (or ECW/ICW) is a cellular determinant of the TBW/FFM ratio in adults.<sup>[10]</sup> If ECW/TBW increases due to any physiological or pathological reason, it may slightly increase the FFM hydration.<sup>[10]</sup> Therefore, any reason for the abnormal water distribution can change the TBW/FFM ratio. A previous study showed that higher ECW/TBW is associated with mortality<sup>[27]</sup> and was also suggested by our ROC analysis. In our study, the discriminatory power of TBW/FFM for mortality was slightly better than that of ECW/TBW.

Sarcopenia is a common complication in HD patients and results in increased ECW/TBW ratios, that is, fluid overload status.<sup>[28]</sup> However, in our study, there was no significant difference in sarcopenia between the 2 groups, and it is possible that these discrepancies were due to the size of the study population, and further study should be confirmed.

Our study had several limitations. First, our study did not examine the dynamic changes in the TBW/FFM ratio and

laboratory indicators. Second, this was a single-center study with a small sample size and a short follow-up time.

# 5. Conclusion

In summary, a higher TBW/FFM ratio was associated with overhydration and malnutrition. Elevated ECW/TBW was the most important determinant of a higher TBW/FFM ratio. High TBW/ FFM can be used as a valuable prognostic index for predicting all-cause mortality in HD patients.

#### **Author contributions**

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