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A comparison of fluid status determination using bioelectric impedance and the isotope dilution method in hemodialysis and peritoneal dialysis patients

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ABSTRACT

We aimed to compare fluid status as determined by multifrequency bioimpedance spectroscopy (MF-BIS, Xitron 4200, USA) with that determined by the isotope dilution method among a contemporary Chinese cohort. Healthy Chinese subjects (HS, $n = 30$) were recruited in Zhengzhou. Hemodialysis (HD, $n = 49$) and peritoneal dialysis (PD, $n = 48$) patients were screened at the First Affiliated Hospital of Zhengzhou University. Total body water (TBW) and extracellular water (ECW) were measured by deuterium (TBW_D) and bromide (ECW_{Br}) dilution, respectively, and by MF-BIS using the Moissl equation (ME). The results of MF-BIS were compared to the reference method by Pearson analysis and Bland–Altman analysis in the three groups. The accuracy of overhydration as determined by MF-BIS was analyzed by receiver operating characteristic (ROC) curves. The TBW_D and TBW_{ME} values were 34.67 ± 7.31 and 35.41 ± 5.76 L, 37.30 ± 8.58 and 37.02 ± 8.10 L, and 38.61 ± 10.02 and 38.44 ± 7.59 L in the HS, HD and PD groups, respectively. The ECW_{Br} and ECW_{ME} values were 14.88 ± 3.33 and 15.53 ± 2.39 L, 16.24 ± 5.08 and 16.90 ± 3.93 L, and 19.08 ± 6.41 and 18.23 ± 3.61 L in the HS, HD and PD groups, respectively. The mean bias between TBW_D and TBW_{ME} was -0.74 L, 0.28 L, and 0.17 L in the HS, HD and PD groups, respectively. The mean bias between ECW_{Br} and ECW_{ME} was -0.65 L, -0.66 L, and 0.85 L in the HS, HD and PD groups, respectively. Compared to the ECW_{Br}/TBW_D ratio, the area under the ROC curve (AUC) of the ECW_{ME}/TBW_{ME} ratio for the diagnosis of overhydration was 0.76 and 0.68 in the HD and PD groups, respectively. In summary, MF-BIS with ME could be used in Chinese HD and PD patients.

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Introduction

Fluid status, which is a specific value of the relative fluid volume in a patient's body, can be categorized as one of three states: fluid overload, normal fluid or fluid depletion. The hydration state of patients is an important factor in hemodialysis (HD) and peritoneal dialysis (PD). HD and PD patients may experience wide variations between fluid overload and fluid depletion [1–3]. An excessive hydration state in patients undergoing dialysis is associated with the development of congestive heart failure and a higher mortality [4–6]. Wizemann et al. [6] showed that patients with a hydration level above 2.5 L had a significantly increased risk of mortality. Therefore, estimating body water content is important for dialysis patients. However, accurately assessing fluid status is a major clinical challenge in HD and PD patients.

Bioimpedance analyses, including single-frequency bioimpedance analysis (SF-BIA) and multifrequency bioimpedance spectroscopy (MF-BIS), are widely used to calculate extracellular water (ECW) and total body water (TBW) in dialysis patients. In addition, a ratio of ECW to TBW (ECW/TBW) greater than 0.4 has been proposed as an index of volume status in hemodialysis patients [7]. The MF-BIS equations for evaluating body composition are based on the Cole-Cole model and the Hanai principle: the Xitron equations (XE) [8,9] and the Moissl equations (ME) [10]. The ME were developed by including body mass index (BMI) when calculating intracellular water (ICW) using data from 152 subjects (120 healthy subjects and 32 dialysis patients) from three different centers [10]. BIS with ME provided an accurate estimation of TBW and ECW without systematic bias in wrestlers [11]. Our previous study revealed that ME

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provided a better point estimation of ICW and TBW in hemodialysis patients [12]. Chamney et al., [13] using their three-room model based on data from healthy individuals, proposed a calculation model for excess fluid mass (M_{EXF}) based on weight, ECW and ICW. The hydration state defined by M_{EXF} was shown to be a predictor of mortality in a mixed cohort of PD and HD patients [14].

Isotope dilution is considered the gold standard for measuring body water compartments in healthy and unhealthy individuals. Usually, deuterium and bromide dilution techniques are used as the criterion methods for measuring TBW and ECW, respectively. Recently, Gregorio P. Milani [15] and Jochen G. Raimann [16] used the isotope dilution method as a direct estimation approach to assess the accuracy of the bioimpedance method in pediatric and adult hemodialysis patients. However, there are few studies about determining hydration state using the isotope dilution method in Chinese PD and HD patients.

In the current study, we investigated the accuracy of estimating fluid status with MF-BIS (ME) and the isotope dilution method in Chinese populations (including HS, HD patients, and PD patients) and to explore whether the hydration state calculated using MF-BIS (ME) could be used in Chinese HD and PD patients.

Materials and methods

Patients and healthy subjects

From September 2018 to August 2019, hemodialysis and peritoneal dialysis patients were screened in the Department of Nephrology and hemodialysis center of The First Affiliated Hospital of Zhengzhou University. The following inclusion criteria were used: receiving maintenance hemodialysis or peritoneal dialysis; dialysis vintage $\geq$3 months; age $\geq$18 years and $<$80 years; and signed informed consent. The following exclusion criteria were used: patients with cirrhosis or tumors; patients with heart implants or pacemakers; patients with amputation or paralysis; and patients without signed informed consent.

Healthy subjects were recruited from September 2019 to October 2019. The following inclusion criteria were used: age $\geq$18 years old and $<$80 years old; normal physical examination and laboratory test results; and signed informed consent. The following exclusion criteria were used: history of major diseases such as kidney, liver, respiratory system, and cardio-cerebrovascular system; history of hypertension; history of diabetes; amputation or paralysis; and without signed informed consent.

The medical ethics committee of The First Affiliated Hospital of Zhengzhou University approved this study (approval number 2018-KY-36). Written informed consent was obtained from all of the patients and healthy subjects.

Bioelectric impedance analysis method

The height and weight of each participant were measured by an Height weight meter (HNH-318, Omron, Japan). Bioelectrical impedance measurements were performed in a standard Xitron 4200 (Multifrequency, Xitron Technologies Inc., San Diego, CA, USA) while the patient was lying supine on a flatbed. The patients removed all metal objects, lay on their back for at least 5 min, performed a double arm outreach, and spread their lower limbs to double their natural separation. Hemodialysis patients were evaluated on nondialysis days, and peritoneal dialysis patients were in the nondialysis state without dialysis fluid in the abdominal cavity. All patients were in a fasting state on the morning of the experiment until all of the measurements were completed. For hemodialysis patients with an arteriovenous fistula, we measured the contralateral limb. We took right-side body measurements of the healthy subjects, peritoneal dialysis patients and hemodialysis patients using central venous catheters. Imperceptible currents were introduced at distal electrodes on the hands (proximal to the phalangeal-metacarpal joint in the middle of the dorsal side of the hand) and the feet (proximal to the transverse arch on the superior side of the foot). Resistances were measured by proximal electrodes (on the wrist midway between the styloid process and on the ankle midway between the malleoli). The resistance of the extracellular component (R_e) was equivalent to R_0, and the resistance of the intracellular components (R_i) was calculated as $1/((1/R_\infty)-(1/R_0))$. The water compartment volumes were directly calculated from the resistance values using the Moissl equations (MEs) (Equations 1–5).

$$ECW_{ME} = K_{ECW}\left(\frac{H^2.\sqrt{Wt}}{Re}\right)^{\frac{2}{3}} \tag{1}$$

$$ICW_{ME} = K_{ICW}\left(\frac{H^2.\sqrt{Wt}}{Ri}\right)^{\frac{2}{3}} \tag{2}$$

$$K_{ECW} = \frac{0.188}{BMI} + 0.2883 \tag{3}$$

$$K_{ICW} = \frac{5.8758}{BMI} + 0.4194 \tag{4}$$

$$TBW_{ME} = ECW_{ME} + ICW_{ME} \tag{5}$$

ECW_{ME}, ICW_{ME} and TBW_{ME} are the extracellular water, intracellular water and total body water volumes, respectively, as determined by MF-BIS with the Moissl equation (ME, liters). H is the body height (centimeters), and Wt is the body weight (kilograms). R_e is the resistance of the extracellular component, and R_i is the resistance of the intracellular components. BMI is the body mass index (kg/m^2). K_{ECW} and K_{ICW} are the variable coefficients based on the individual's BMI.

M_{EXF} is the excess fluid volume (liters) and is calculated by Equation (6) [13].

$$M_{EXF} = 1.136 * ECW - 0.430 * ICW - 0.114 * Wt \quad (6)$$

ECW and ICW were calculated by ME or isotope dilution (liters). Wt is the body weight (kilograms).

Isotope dilution method

Hemodialysis patients were evaluated on nondialysis days, and peritoneal dialysis patients were in the nondialysis state without dialysis fluid in the abdominal cavity. All patients were in a fasting state on the morning of the experiment until all measurements were completed. In the early morning after an overnight fast, patients received an orally administered dose of D_2O (MKCB1666A, isotopic purity, 99.9%; Sigma Chemicals, St. Louis, MO, USA) of 0.4 g/kg and NaBr (MKCD7434, isotopic purity, 99.9%; Sigma Chemicals, St. Louis, MO, USA) of 0.01 g/kg [17]. Enrichments of D_2O and NaBr in the body fluid were measured in the serum. Immediately before D_2O and NaBr intake, The first blood sample was collected before D_2O and NaBr intake immediately. After an equilibration time of 4 h, a second blood sample was collected. Food intake was not allowed until the second blood sample was collected, but drinking a small amount of water was allowed. All patients took their medications just before or during the measurements. The timeline of the procedures is summarized in Figure 1.

Sample analysis and calculations

Plasma samples were stored at −80 °C in the biological sample library of Zhengzhou University First Affiliated Hospital until analysis.

Samples of deuterium dilution were analyzed at the Huake Gray Stable Isotope Laboratory, Shenzhen, China. Deuterium dilution was determined by Flash 2000 HT-Elemental Analyzer isotope ratio mass spectrometry (Finnigan Delta V Advantage). Based on the theory that samples generated H_2 after high-temperature cracking in an elemental analyzer, the mass spectrometer detected the ratio of $^2H(D)$ to ^1H in H_2, compared the result with international standards, and then calculated the sample δ^2H (δD) ratio value (measurement accuracy: δ^2H (δD): $\pm$ <1 ‰). The TBW values were obtained by the following calculation (Equation 7) [18]:

$$TBW_D = \frac{A}{B} \times 0.928 \quad (7)$$

TBW_D is the total body water volume by D_2O (liters). A is the quantity of D_2O administered in grams, and B is the concentration difference of D_2O (after the D_2O intake minus before). The correction coefficient was 0.928, which takes into account that D_2O is involved in H/D exchange processes within the body [18].

Samples of bromide dilution were analyzed at the Modern Analysis Center of Zhengzhou University. Bromide dilution was determined by Optimass 9500 (ICP time-of-flight mass spectrometer, GBC Scientific Instrument Co., Ltd., Australia). The concentration of the bromide dilution was measured by quantitative methods using an internal standard working curve method. Extracellular water can be estimated from the corrected bromide space (CBS), which was calculated according to the following formula (Equation 8) [19]:

$$CBS = \text{Br dose}\,\frac{\text{mmol}}{\text{Br}}\ \text{in plasma}\left(\frac{\text{mmol}}{\text{l}}\right) \times 0.90 \times 0.95 \times 0.94 \quad (8)$$

CBS is the corrected bromide space, which represents the ECW value calculated by bromide dilution; 0.90 is the correction factor for the distribution of bromide in nonextracellular sites (principally red blood cells); 0.95 is the correction factor for the Donnan equilibrium; and 0.94 is the correction factor for the concentration of water in plasma, which is approximately 94% [19].

Statistical analysis

All data are expressed as the mean ± standard deviation or median (interquartile range) according to the distribution. Group differences were analyzed using one-way ANOVA (normal distribution) or the Mann–Whitney test

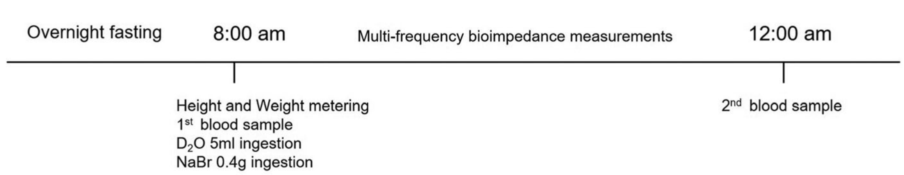

Figure 1. Time schedule summary of protocol procedures on the test day. *Abbreviations*: D_2O: deuterated water; NaBr: sodium bromide.

(nonnormal distribution). Correlations between body compartments measured by different methods were estimated using Pearson correlations. A p value <0.05 was considered significant. Bland–Altman plots were used to visually assess the agreement between the different TBW and ECW calculation methods. Bias was defined as the mean difference between the index and reference tests, and precision was defined as the 95% standard deviation (SD) of bias. A receiver operating characteristic (ROC) curve was used to evaluate the diagnostic value of M_{EXF} for fluid overload status in dialysis patients. Statistical analysis was performed with SPSS Statistics 26.0. Figures were developed with GraphPad Prism 8.

Results

Characteristics of healthy subjects and patients

There were one hundred twenty-seven participants in our study, including thirty healthy subjects (18 men), forty-nine hemodialysis patients (33 men), and forty-eight peritoneal dialysis patients (26 men). The HD patients were prescribed as follows, 3–4 treatments/week, treatment time 4 h, ultrafiltration rate 848.2 ± 180.4 mL/h, blood flow rate 252.5 ± 26.9 mL/min. The PD patients were all on CAPD and the number of exchanges per day was 3.7 ± 0.7(2–5). And 31 PD patients using 1.5% of glucose in dialysate, 13 PD patients using 1.5% and 2.5% of glucose and three patients using 2.5% of glucose in dialysate. The patient characteristics are presented in Table 1. Twenty-five hemodialysis patients lacked total urea clearance index (kt/v) values, but all other data were complete. Age, height, weight, body mass index (BMI), body surface area (BSA), gamma-glutamyl transpeptidase (GGT) level and alkaline phosphatase (ALP) level were not different among the HS, HD and PD groups ($p > 0.05$). Serum creatinine (Scr), alanine aminotransferase (ALT), glutamic oxaloacetic transaminase (AST), total protein (TP), albumin protein (ALB), globulin (GLB), white blood cell (WBC), red blood cell (RBC), hemoglobin (Hb), platelet (PLT), neutrophil (Neut) and lymphocyte (Lymph) levels showed significant differences among the HS, HD and PD groups ($p < 0.05$). Scr, ALT, AST, TP, ALB, GLB, WBC, RBC and Hb levels showed significant differences between the HD and PD groups ($p < 0.05$).

Fluid status of healthy subjects

As shown in Table 2, the ECW_{Br} volume of the healthy subject group was 14.88 ± 3.33 (9.73–22.31) L and the

Table 1. Patient characteristics of three groups.

Characteristic	Healthy subjects ($n = 30$)	HD ($n = 49$)	PD ($n = 48$)	p
Gender, male	18 (30)	33 (49)	26 (48)	*>0.05*
Age, y	44.13 ± 11.64 (25–63)	45.76 ± 11.48 (22–67)	46.63 ± 11.01 (23–65)	*>0.05*
Height, cm	167.70 ± 8.00 (153.0–183.0)	166.4 ± 9.10 (137.0–183.0)	165.16 ± 8.05 (146.0–181.0)	*>0.05*
Weight, kg	69.95 ± 12.14 (44.6–95.0)	69.10 ± 14.34 (42–113)	64.14 ± 9.34 (46.5–85)	*>0.05*
BMI, kg/m^2	24.88 ± 4.25 (16.4–35.7)	24.83 ± 4.04 (17.83–34.73)	23.47 ± 2.74 (18.8–30.20)	*>0.05*
BSA, kg/m^2	1.89 ± 0.19 (1.5–2.3)	1.86 ± 0.23 (1.3–2.5)	1.8 ± 0.16 (1.5–2.1)	*>0.05*
Scr, (20-115)umol/L	70.43 ± 12.81 (49–99)	901.12 ± 272.62 (391–1656)*	1046.98 ± 275.54 (460.9–1842)*‡	*<0.05*
kt/v	–	1.12 ± 0.29 (0.42–1.76)	1.7 ± 0.38 (0.96–2.67)‡	–
Dialysis vintage(months)		12 (4.5, 24)	6 (3, 13.7)	–
Total ultrafiltration volume (L/week)		10.5 ± 2.7 (5.7–17.6)	1.4 (-2.6, 6.1)	–
ALT, (0–40)U/L	23.29 ± 19.08 (9.0–101.0)	14.59 ± 10.95 (5.0–62.0)*	19.89 ± 12.16 (6.0–53.0)‡	*<0.05*
AST, (0–40)U/L	21.27 ± 9.03 (10.0–55.0)	14.16 ± 6.69 (6.0–39.0)*	18.17 ± 7.49 (6.0–39.0)‡	*<0.05*
GGT, (0–58)U/L	25.35 ± 13.64 (9.0–66.0)	32.23 ± 28.61 (8.0–155.0)	22.23 ± 13.19 (8.0–69.0)	*<0.05*
ALP ,(35–105)U/L	71.30 ± 12.90 (45.0–95.0)	80.06 ± 58.37 (29.0–431.0)	74.90 ± 39.36 (31.0–266.0)	>0.05
TP, (60–85) g/L	75.27 ± 4.19 (65.7–85.8)	68.17 ± 7.04 (55.3–88.1)*	56.39 ± 6.61 (42.3–72.6)*‡	*<0.05*
ALB, (35–55)g/L	47.67 ± 2.93 (40.6–51.2)	41.47 ± 4.21 (32.8–55.6)*	32.75 ± 4.42 (23.9–44.0)*‡	*<0.05*
GLB, (20–35)g/L	27.60 ± 3.80 (18.9–43.9)	26.69 ± 5.49 (17.2–43.9)	23.65 ± 3.97 (13.8–35.2)*‡	*<0.05*
WBC, (3.5–9.5)10^9/L	6.48 ± 1.17 (3.78–8.40)	6.17 ± 1.60 (3.40–10.80)	5.3 ± 1.57 (2.43–8.89)*‡	*<0.05*
RBC,(3.8–5.1)10^{12}/L	4.73 ± 0.41 (3.83–5.26)	3.75 ± 0.69 (2.45–5.88)*	3.26 ± 0.68 (2.15–5.06)*‡	*<0.05*
Hb, (115–150) g/L	145.26 ± 11.28 (129.0–165.0)	115.06 ± 18.96 (75.0–155.2)*	99.05 ± 18.67 (66.0–151.6)*‡	*<0.05*
PLT, (125–350)10^9/L	234.13 ± 49.62 (124.0–331.0)	192.55 ± 64.07 (108.0–346.0)*	170.46 ± 56.95 (53.0–280.0)*	*<0.05*
Neut, (1.8–6.3)10^9/L	3.64 ± 0.97 (1.60–5.31)	4.32 ± 1.25 (2.22–8.36)*	3.62 ± 1.37 (1.65–7.51)*	*<0.05*
Lymph,(1.1-3.2)10^9/L	2.06 ± 0.54 (1.31–3.74)	1.27 ± 0.50 (0.27–2.94)*	1.04 ± 0.34 (0.30–1.95)*	*<0.05*
Cause of ESRD [n(%)]	–	–	–	–
Chronic glomerulonephritis	–	32 (65.31)	31 (64.58)	–
Hypertensive renal damage	–	2 (4.08)	7 (14.58)	–
Diabetic nephropathy	–	7 (14.29)	0 (0)	–
Others	–	8 (16.33)	10 (20.83)	–

Data were express as mean ± SD or median (interquartile range).
Abbreviations: BMI: body mass index; BSA: body surface area; kt/v: total Kt/v. Age, height, weight, BMI, BSA, GGT, and ALP had no difference between NC, HD, and PD groups ($p > 0.05$). Scr, ALT, AST, TP, ALB, GLB, WBC, RBC, Hb, PLT, neut, and lymph showed statistical significance between NC, HD, and PD groups ($p < 0.05$). Scr, ALT, AST, TP, ALB, RBC, Hb, neut, and lymph showed statistical significance between NC and HD groups (*$p < 0.05$). Scr, TP, ALB, GLB, WBC, RBC, Hb, PLT, neut, and lymph showed statistical significance between NC and PD groups (*$p < 0.05$). Scr, kt/v, ALT, AST, TP, ALB, GLB, WBC, RBC, and Hb showed statistical significance between HD and PD groups (‡$p < 0.05$). Italic values are statistically significant at $p < 0.05$.

Table 2. Result of TBW, ECW, OH and ECW/TBW of three groups.

Variable	Healthy subjects ($n=30$)	HD ($n=49$)	PD ($n=48$)	p
ECW_{Br},L	14.88 ± 3.33 (9.73–22.31)	16.24 ± 5.08 (9.36–39.83)	19.08 ± 6.41 (10.56–46.88)*‡	*<0.05*
TBW_D,L	34.67 ± 7.31 (20.64–55.89)	37.30 ± 8.58 (21.97–58.74)*	38.61 ± 10.02 (25.16–75.20)*‡	*>0.05*
M_{EXF}-dilution,L	0.41 ± 3.48 (-6.84–8.29)	1.52 ± 6.44 (-12.53–29.79)	5.97 ± 8.43 (-17.66–34.35)*‡	*<0.05*
ECW_{Br}/TBW_D	0.43 ± 0.06 (0.30–0.55)	0.44 ± 0.10 (0.21–0.75)	0.50 ± 0.12 (0.17–0.84)*‡	*<0.05*
ECW_{ME},L	15.53 ± 2.39 (11.36–19.43)	16.90 ± 3.93 (9.25–27.18)	18.23 ± 3.61 (11.66–27.53)*	*<0.05*
TBW_{ME},L	35.41 ± 5.76 (23.88–47.21)	37.02 ± 8.10 (18.74–55.54)	38.44 ± 7.59 (25.56–56.51)	*>0.05*
M_{EXF}-ME,L	1.12 ± 0.77 (-0.70–2.36)	2.67 ± 2.41 (-2.07–8.42)*	4.71 ± 2.37 (-0.20–10.43)*‡	*<0.05*
ECW_{ME}/TBW_{ME}	0.44 ± 0.02 (0.40–0.49)	0.46 ± 0.04 (0.36–0.54)*	0.48 ± 0.04 (0.39–0.53)*‡	*<0.05*

Data were express as Mean ± SD or median (interquartile range).
Abbreviations: ECW: extracellular water; TBW: total body water; M_{EXF}: excess fluid mass; ECW/TBW: ECW to TBW ratio; ECW_{Br}: extracellular water by bromide dilution; TBW_D: total body water by deuterium dilution. SD: standard deviation. TBW_{ME}, ECW_{ME}, $M_{EXF\ ME}$, body water by MF-BIS (ME equation) method; $M_{EXF\ gold}$, excess fluid mass calculated by ECW_{Br} and TBW_D.
TBW_D and TBW_{ME} had no difference between NC, HD, and PD groups ($p > 0.05$). ECW_{Br}, $M_{EXF\ gold}$, ECW_{Br}/TBW_D, ECW_{ME}, $M_{EXF\ ME}$, and ECW_{ME}/TBW_{ME} showed statistical significance between NC, HD and PD groups ($p < 0.05$). TBW_D, $M_{EXF\ ME}$, and ECW_{ME}/TBW_{ME} showed statistical significance between NC and HD groups (*$p < 0.05$). ECW_{Br}, TBW_D, $M_{EXF\ gold}$, ECW_{Br}/TBW_D, ECW_{ME}, $M_{EXF\ ME}$, and ECW_{ME}/TBW_{ME} showed statistical significance between NC and PD groups (*$p < 0.05$). ECW_{Br}, TBW_D, $M_{EXF\ gold}$, ECW_{Br}/TBW_D, $M_{EXF\ ME}$, and ECW_{ME}/TBW_{ME} showed statistical significance between HD and PD groups (‡ $p < 0.005$). Italic values are statistically significant at $p < 0.05$.

ECW_{ME} volume was 15.53 ± 2.39 (11.36–19.43) L. Using the Pearson analysis method, the correlation between the ECW_{Br} and ECW_{ME} volumes was determined to be statistically significant ($r = 0.62$, $p < 0.05$) (Figure 2(A)). The mean difference between the ECW_{Br} and ECW_{ME} volumes by Bland–Altman analysis was −0.65 L (95% limits of agreement, −5.8 to 4.5 L), and the 95% CI was −1.6 to 0.28 L (Figure 2(B)).

In the HS group, the TBW_{ME} volume was 35.41 ± 5.76 L, and the TBW_D volume was 34.67 ± 7.31 L (Table 2). TBW_D volume was significantly correlated with TBW_{ME} volume ($r = 0.75$, $p < 0.05$) (Figure 2(C)). The Bland–Altman plot is shown in Figure 2(D). The mean difference between the TBW_D and TBW_{ME} volumes was −0.74 L (95% limits of agreement, −10.26 to 8.78 L), and the 95% confidence interval (CI) was −2.48 to 1.0 L.

Fluid volume in hemodialysis patients

In the HD group, the ECW_{Br} volume was 16.24 ± 5.08 L and the ECW_{ME} volume was 16.90 ± 3.93 L (Table 2). Pearson analysis showed that there was a moderate correlation between the ECW_{ME} and ECW_{Br} volumes ($r = 0.75$, $p < 0.05$) (Figure 3(A)). The mean difference between the ECW_{Br} and ECW_{ME} volumes was −0.66 L (95% limits of agreement, −7.226 to 5.908 L), and the 95% CI was −1.62 to 0.3 L.

As shown in Table 2, the TBW_{ME} volume of the patients in the HD group was 37.02 ± 8.10 L, and the TBW_D volume was 37.30 ± 8.58 L. There was a moderate correlation between the volumes calculated by the two different methods ($r = 0.69$, $p < 0.001$) (Figure 3(C)). The mean difference between the TBW_D and TBW_{ME} volumes was 0.2807 L (95% limits of agreement, −12.67 to 13.23 L), and the 95% CI was −1.56 to 2.12 L (Figure 3(D)). The TBW_D volume of the patients in the HD group was significantly higher than that of the healthy subjects (37.30 ± 8.58 vs. 34.67 ± 7.31, $p < 0.05$).

Fluid volume of peritoneal dialysis patients

In the PD group, the ECW_{Br} volume was 19.08 ± 6.41 L, and the ECW_{ME} volume was 18.23 ± 3.61 L. There was a moderate correlation between the ECW_{ME} and ECW_{Br} volumes ($r = 0.5737$, $p < 0.001$) (Figure 4(A)). The mean difference between the ECW_{ME} and ECW_{Br} volumes was 0.85 L (95% limits of agreement, −9.446 to 11.15 L), and the 95% CI was −0.63 to 2.34 L (Figure 4(B)). The ECW_{Br} and ECW_{ME} volumes were significantly different among the patients in the healthy subject, HD, and PD groups (*$p < 0.05$).

The TBW_{ME} volume was 38.44 ± 7.59 L, and the TBW_D volume was 38.61 ± 10.02 L (Table 2). A mild correlation existed between the TBW_D and TBW_{ME} volumes in the PD group ($r = 0.34$, $p < 0.05$) (Figure 4(C)). The mean difference between the TBW_D and TBW_{ME} volumes in the PD group was 0.17 L (95% limits of agreement, −20.07 to 20.41 L), and the 95% CI was −2.75 to 3.09 L (Figure4(D)). TBW_D volume was significantly different among the patients in the healthy subject, HD, and PD groups ($p < 0.05$).

Excess fluid mass (M_{EXF}) and ECW/TBW ratio of dialysis patients

The M_{EXF} and ECW/TBW ratios are shown in Table 2. M_{EXF}-dilution, M_{EXF}-ME, ECW_{Br}/TBW_D and ECW_{ME}/TBW_{ME} had significant differences among the HS, HD and PD groups ($p < 0.05$). Receiver operating characteristic (ROC) curves were used to analyze the diagnostic value of MF-BIS. As shown in Figure 5, the AUC values were 0.82 for M_{EXF} and 0.76 for the ECW/TBW ratio in the HD group. For the PD group, the AUC values were 0.77 for

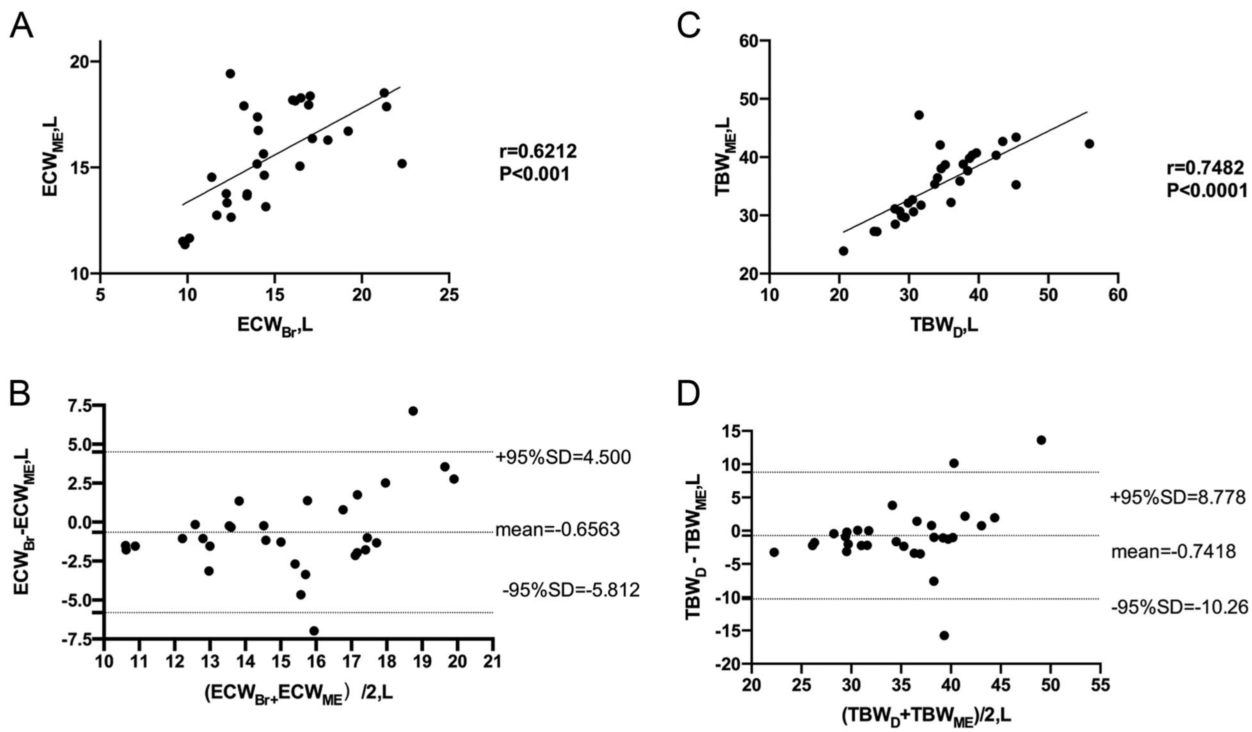

Figure 2. The correlation and consistency of ME compared with isotope dilution in predicting the ECW and TBW of the HS group. The correlation between ECW (A) and TBW (C) by the two methods was estimated using Pearson product moment correlations. p Value $<$ 0.05 was considered significant. Regarding the correlation between ECW_{ME} and ECW_{Br}, the r value of the HS group was 0.6212 ($p < 0.001$), and the r value of the correlation between TBW_{ME} and TBW_D was 0.7482 ($p < 0.001$). The Bland–Altman plots show consistency between ME and the deuterium dilution. The dashed lines indicate the bias and the 95% limits of agreement. For ECW, the 95% limits of agreement (B) were -5.812 to 4.500 L, and for TBW, they were -10.26 to 8.78 L (D). Their biases were 0.6563 (ECW) and -0.7418 (TBW).

M_{EXF} and 0.68 for the ECW/TBW ratio. The cutoff value of M_{EXF} in the HD group was 3.44 L, and the cutoff value of the ECW/TBW ratio in the HD group was 0.44. The cutoff value of the PD group was 3.92 L for M_{EXF} and 0.44 for the ECW/TBW ratio, respectively.

The overhydration rate between HD and PD patients were compared by BIS and dilution method (the definition of overload was OH/ECW (OH/ECW $\geq$0.13) for females and (OH/ECW $\geq$0.15) for males) (Table 3). The overhydration rate of PD patients was more than HD patients with the both two methods.

Discussion

The accurate assessment of fluid status is a major clinical challenge. In our study, we first used MF-BIS (ME) and the isotope dilution method to estimate fluid status in a contemporary Chinese cohort and found that ME had moderate accuracy in Chinese HS and HD patients. However, ME lacks less accuracy in calculating body water in PD patients compared to HS and HD patients. In summary, the hydration state calculated using ME could be used in Chinese HD and PD patients, although the accuracy needs to be improved.

Our study showed that MF-BIS had a better correlation and good agreement in healthy subjects. To our knowledge, this is the first study comparing ME and isotope dilution in healthy Chinese subjects. Our results showed that the mean difference between the TBW_D and TBW_{ME} volumes was $-0.74\,L \pm 0.89$. Moissl et al. [10] reported that the result of TBW calculation in German healthy subjects was -0.5 ± 2.1 L for TBW_D – TBW_{ME}. The mean difference between the ECW_{Br} and ECW_{ME} volumes by Bland–Altman analysis of our data was -0.66 ± 0.48 L, and the result of ECW calculation in healthy subjects was -0.7 ± 1.2 L for ECW_{Br} – ECW_{ME} in Moissl et al. [10] Therefore, our results in healthy subjects were consistent with those reported by Moissl et al. [10] ME could be used to calculate the TBW and ECW volumes in healthy Chinese people.

In the HD group of our study, TBW_{ME} and TBW_D volumes were moderately correlated, and ECW_{ME} and ECW_{Br} volumes were also moderately correlated. The mean difference between the two methods was 0.28 [95% CI, -1.56 to 2.12] L for TBW and -0.66 [95% CI,

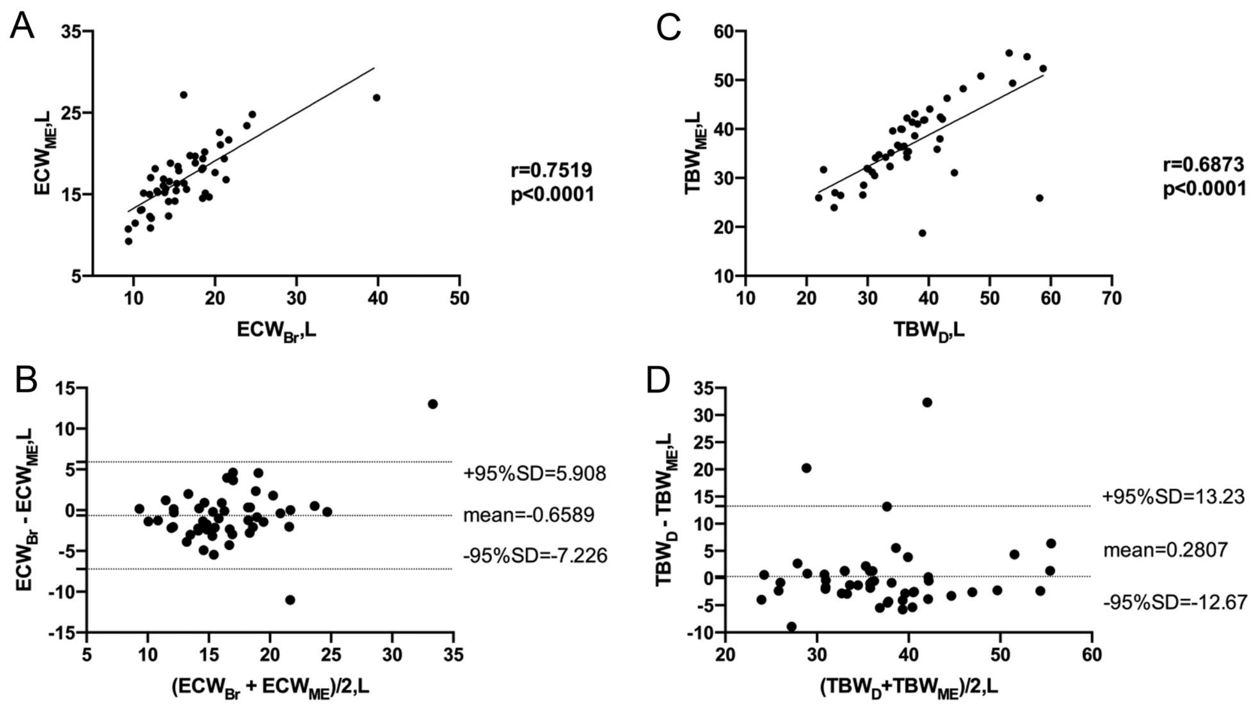

Figure 3. The correlation and consistency of ME compared with isotope dilution in predicting the ECW and TBW of the HD group. The correlation between ECW (A) and TBW (C) by the two methods was estimated using Pearson product moment correlations. A p value < 0.05 was considered significant. Regarding the correlation between ECW_{ME} and ECW_{Br}, the r value was 0.7519 ($p < 0.001$), and the r value the correlation between TBW_{ME} and TBW_D was 0.6873 ($p < 0.001$). The Bland–Altman plots show consistency between ME and the deuterium dilution. Dashed lines indicate bias and 95% limits of agreement. The 95% limits of agreement were -7.226 to 5.908 L (ECW) (B) and -12.67 to 13.23 L (TBW) (D). Their biases were 0.6589 (ECW) and 0.2807 (TBW).

−1.62 to 0.30] L for ECW. The difference between the two methods was almost the same in HD patients and healthy subjects. The bias was in accordance with Raimann et al., [16] who found that assessments of TBW and ECW by dilution techniques and BIS in HD patients did not differ significantly (mean difference, 1.9 [95% CI, −1.3 to 5.1] L for TBW and −0.2 [95% CI, −1.9 to 1.16] L for ECW) and that the bioimpedance measurements had high reproducibility (coefficients of variation, 1.2 and 0.2% for TBW and ECW, respectively). MF-BIS (ME) could be used to calculate the TBW and ECW of Chinese hemodialysis patients.

In the PD group of our study, we found a mild correlation between ME and the dilution techniques by the Bland–Altman method. The mean difference between the two methods was 0.17 [95% CI, −2.75 to 3.09] L for TBW and 0.85 [95% CI, −0.64 to 2.34] L for ECW. However, the 95% limits of agreement for TBW and ECW were larger in PD patients than in HD patients and healthy subjects. David Arroyo et al. [20] found that when BIS was applied to PD patients with a full abdomen, fluid overload and ECW were overestimated compared with measurements taken after emptying the abdomen. Fansan Zhu et al. [21] also found that BIS in PD patients with a full abdomen could not estimate the whole body fluid accurately. They found that when 2.19 ± 0.48 L was removed from the peritoneal cavity during draining, 95.2 ± 13.8% of this volume was detected by segmental BIA compared with only 12.5 ± 24.3% detected by whole-body BIA [21]. In our measurements, the abdominal cavity of PD patients was empty of dialysis fluid, which could avoid the nonconformity of resistance and reactance distribution. However, patients with long-term continuous peritoneal dialysis therapy still have residual peritoneal effusion even in a state of peritoneal fluid drainage. This causes the abdominal contents of PD patients to be significantly different from those of HD patients and healthy people. When BIS is performed with a full abdomen, the whole-body impedance is reduced, which results in an overestimation of total body water and ECW [22,23]. We speculated that this might be why BIS lacks accuracy in calculating body water in PD patients compared to HD patients and healthy subjects.

Regarding the use of the BIS method to determine the hydration state compared to the ECW_{Br}/TBW_D ratio, the AUC of the ECW_{ME}/TBW_{ME} ratio for the diagnosis of overexposure was 0.76 and 0.68 in HD and PD patients, respectively. For M_{EXF} as measured by the dilution method, the AUC was 0.82 and 0.77 in HD and PD

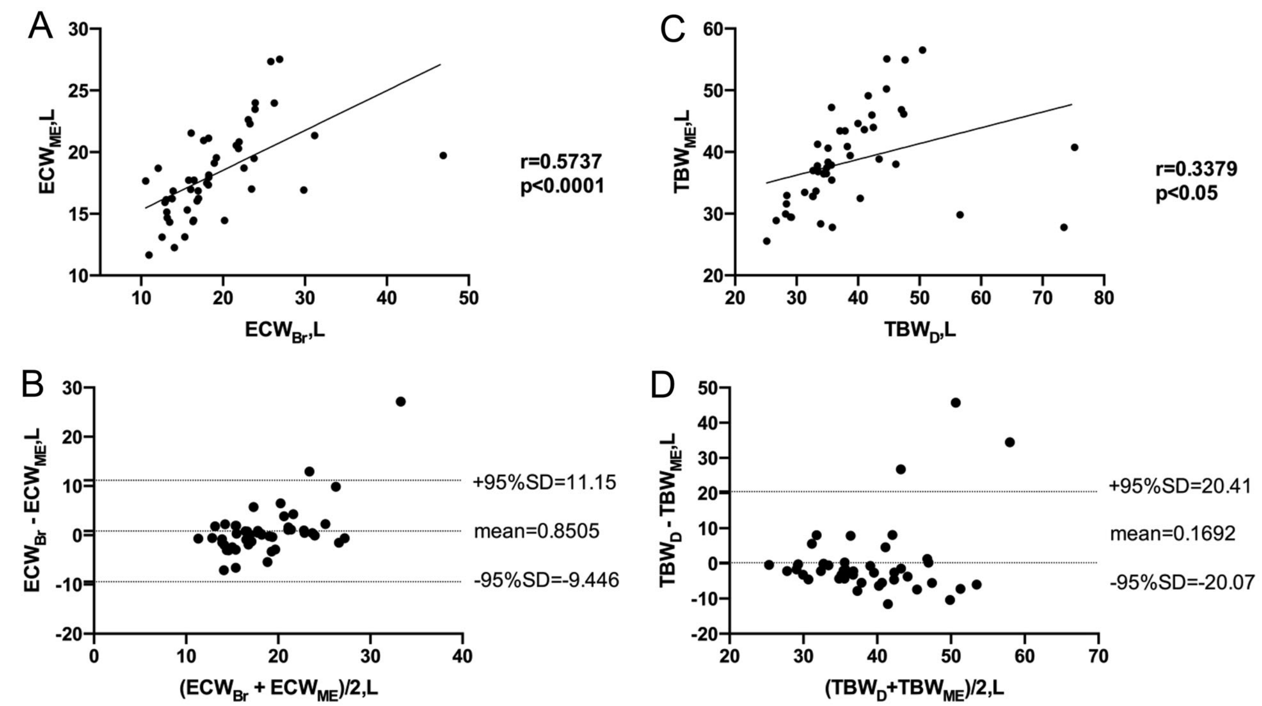

Figure 4. The correlation and consistency of ME compared with isotope dilution in predicting ECW and TBW in the PD group. The correlation between ECW (A) and TBW (C) by the two methods was estimated using Pearson product moment correlations. A p value $<$ 0.05 was considered significant. Regarding the correlation between ECW_{ME} and ECW_{Br}, the r value was 0.5737 ($p < 0.001$), and the r value of the correlation between TBW_{ME} and TBW_D was 0.3379 ($p < 0.001$). The Bland–Altman plots show consistency between ME and the deuterium dilution. Dashed lines indicate the bias and 95% limits of agreement. Their biases were 0.8505 (ECW) and 0.1692 (TBW). Whether ECW (B) or TBW (D), the PD group had the largest 95% limits of agreement (-9.446 to 11.15 L and -20.07 to 20.41 L).

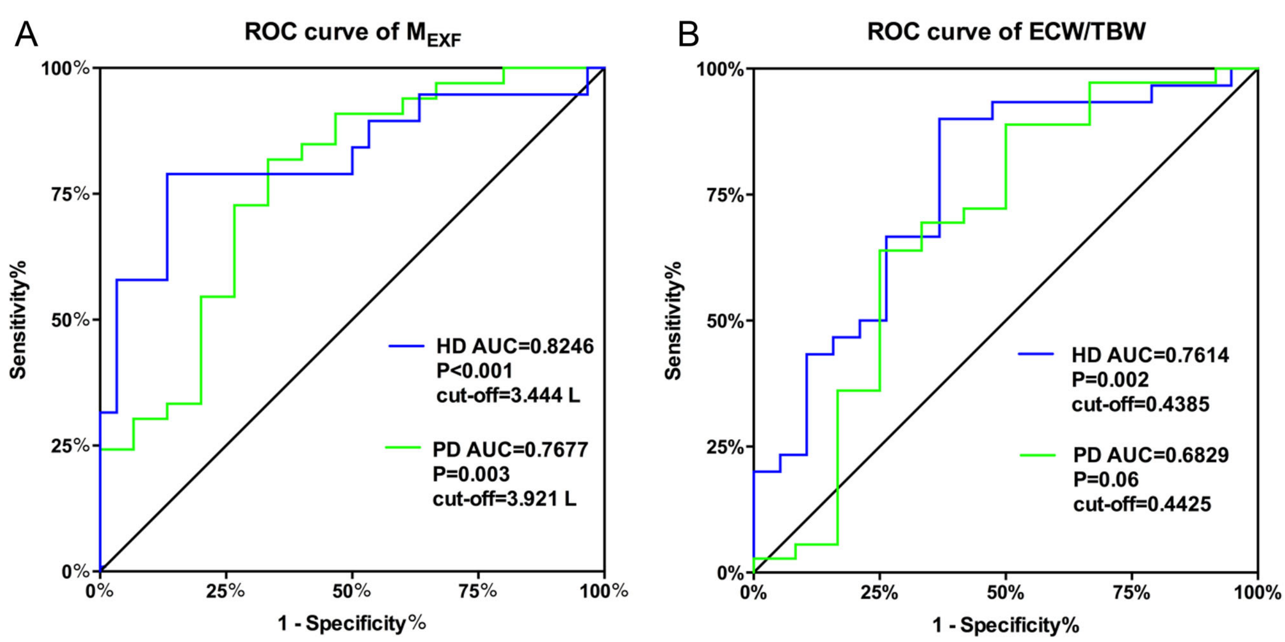

Figure 5. Receiver operating characteristic curve of the M_{EXF} value (A) and the ECW/TBW ratio (B) in dialysis patients. A: ROC curve of M_{EXF}. The blue line represents the HD group, and the green line represents the PD group. The AUC of the HD group was 0.8246 ($p < 0.001$), and the cutoff value was 3.444 L. The AUC of the PD group was 0.7677 ($p = 0.003$), and the cutoff value was 3.921 L. B: ROC curve of the ECW/TBW ratio. The blue line represents the HD group, and the green line represents the PD group. The AUC of the HD group was 0.7614 ($p = 0.002$), and the cutoff value was 0.4385. The AUC of the PD group was 0.6829 ($p = 0.06$), and the cutoff value was 0.4425.

Table 3. The overhydration rate between HD and PD patients by different method.

BIS method	The number of overhydation	The number of non-overhydation	Total numbers	Diluton method	The number of overhydation	The number of non-overhydation	Total numbers
HD patients	24	25	49	HD patients	30	29	49
PD patients	39	9	48	PD patients	33	15	48
	63	34			63	44	
	χ^2=11.09	$p < 0.05$			χ^2=7.63	$p < 0.05$	

patients, respectively. Our results suggest that hydration state calculation using the BIS method could be used in Chinese HD and PD patients. However, the accuracy needs to be improved.

There are several limitations of our study. The first limitation is the small number of patients enrolled. However, it should be noted that the total number of participants is similar to that in previous studies [16]. Our sample size was larger than that in the study by Gregorio P. Milani et al., [15] which included 16 dialysis patients. Second, no assessment of residual urine volume was performed to adjust the volume estimation for dilution tracers lost. However, this loss has been previously determined to be negligible [24]. Third, no serial measurements were made to evaluate whether the changes in ECW measured by MF-BIS were correlated with the corresponding changes measured by isotope dilution. Despite the correlation between MF-BIS and isotope dilution, the levels of agreement are rather large, especially in PD patients, limiting its usefulness in clinical practice. It is possible that serial measurements of fluid status by MF-BIS rather than single measurements could be more valuable for the monitoring of hydration status [25,26].

In conclusion, to our knowledge, this is the first study to evaluate the validity of the multifrequency bioimpedance method in Chinese dialysis patients and healthy subjects. We found that MF-BIS with ME could be used in Chinese HD and PD patients, and the equations could be modified to improve the accuracy with Chinese dialysis patients in the future.

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The biological sample library of the First Affiliated Hospital of Zhengzhou University was used until analysis, which provided a −80 °C refrigerator to store our plasma samples. The Huake Gray Stable Isotope Laboratory, Shenzhen, China, analyzed our deuterium dilution samples. The Modern Analysis Center of Zhengzhou University analyzed our bromide dilution samples.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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