Flexible Modeling Approach to Predict Intracellular Water Volume

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Abstract

In clinical practice, accurate prediction of intracellular water (ICW) volume has many constructive applications in addition to its use in the evaluation of nutritional status. Our purpose is to construct a model to predict ICW volume in comparison with the measurement by segmental multifrequency bioelectrical impedance analysis (SMF-BIA). Anthropometric data (age, gender, height, weight), and SMF-BIA were investigated in 45 healthy subjects. ICW volume measured by SMF-BIA (ICW-BIA) was the reference. Predictive performance of ICW volume based on Pierson formula, multiple linear regression (MLR) and generalized additive model (GAM) were evaluated. Predictive ICW volume derived from GAM (21.47 ± 0.57 L) were not significantly different ($p = 0.96$) with ICW-BIA (21.47 ± 0.61 L). GAM also had higher Spearman's rank correlation coefficient (0.95) and smaller root mean square error (1.24) than Pierson formula and MLR. The GAM peak (-0.13) centered most closely to zero with the shortest tails (-2.13 to 2.79) in an empirical cumulative distribution plot. Passing-Bablok regression was described as ICW-BIA = 1.03 × ICW-GAM – 0.69, with 95% confidence interval for slope 0.93 to 1.16 and for intercept -3.43 to 1.36, indicating that GAM and SMF-BIA were interchangeable ($p > 0.10$). GAM outperformed conventionally algebraic equations and could serve as an excellent method for ICW volume prediction in healthy subjects.

Keywords: Generalized additive model, Linear regression, Anthropometry, Intracellular water, Bioelectrical impedance

1. Introduction

Evaluation of intracellular water (ICW) volume has many important applications in clinical care. It can affect the determination of body cell mass, salt balance, nutritional status, renal function, and drug pharmacokinetics. Accurate measurement of ICW volume is thus imperative either in healthy subjects or patients with cardiac dysfunction, renal impairment, malnutrition, or sepsis. Whole-body counting of isotope ^{40}potassium or dilution of radioactive ^{42}potassium can directly measure ICW volume [1]. However, it is not easily achievable in many hospitals due to the requirement of complex equipment with a specialized team in addition to the concern of radiation exposure. Although there are increasingly investigations using bioelectrical impedance analysis (BIA) to measure body

composition in place of complicated techniques of nuclear medicine [2, 3], BIA is not widely available in many dialysis centers. In addition, BIA is still a cumbersome method for patients with or without critical illness because the process may bother patients every time if the clinicians want to evaluate hydrational or nutritional status periodically and then make decisions for further laboratory or therapeutical plans. In contrast, algebraic equations or predictive models for predicting ICW volume are generally accepted for use by clinicians and nutritionists at the bedside [4, 5].

With the help of advances in computer-assisted analysis, it is easy to use the predictive algorithms for clinical application. Traditionally, linear regression uses only continuous variables to perform the analysis under the assumptions of normal distribution and independent relationship among all input variables. However, effects are not often linear and this kind of mathematical model is too simple to fit the complexity of real life. For satisfying the need for accurate prediction, a generalized additive model (GAM) was developed to extend the conventional linear model into a more nonlinear flexibility between predictors and response [6]. In other words, a non-parametric function is estimated for each predictor in the additive model to obtain the best prediction of the dependent variable instead of a single coefficient for each variable.

The purpose of the present study was to evaluate the feasibility of multiple linear regression (MLR) analysis and GAM in quantitatively predicting ICW volume for healthy Taiwaners with segmental multifrequency bioelectrical impedance analysis (SMF-BIA) as the reference method to avoid exposing healthy subjects to additional radiation. To our knowledge, including a literature search in PubMed, this is the first comparative investigation to forecast ICW volume using MLR and GAM.

2. Patients and Methods

2.1 Subjects

The Ethics Committee on Human Studies of Tri-Service General Hospital (Taipei City, Taiwan) approved the study protocol. All subjects provided signed informed consent prior to enrollment in the study. Subjects were excluded if they had any systemic illness such as cardiac, hepatic, or renal diseases, diabetes, or hypertension. Subjects were also excluded if they were taking any medication or had a history of edema formation or edema was found on careful physical examinations. The final study population consisted of 45 healthy Taiwaners.

2.2 Measurements

Anthropometric data of all subjects (age, gender, height, weight) were recorded by the same operator. Specifically, all patients were clothed in underwear with bare feet to receive the anthropometric measurements including body height (BH) measured to the nearest 0.1 cm using a linear height scale and body weight (BW) measured to the nearest 0.1 kg using a digital scale. Mean values from two measurements were used as data.

SMF-BIA is based on the basic principle that resistance of the body to an electrical current applied at low frequencies reflects the extracellular water compartment, whereas at high frequencies the current is conducted in both extracellular and intracellular compartments, reflecting the total body water (TBW) volume. The ICW volume was measured by SMF-BIA (Inbody 3.0, Biospace Co., Seoul, Korea) which uses an eight-polar tactile electrode,

Table 1 The characteristics of 45 healthy subjects

Characteristics	Value or ratio	R_s (95% CI)	p value*
Age (years)	47.84 ± 1.93	-0.29 (-0.54 ~ 0.01)	0.08
Gender (male/female)	18/27	0.83 (0.71 ~ 0.91)	< 0.0001
Body height (cm)	161.49 ± 1.17	0.84 (0.72 ~ 0.91)	< 0.0001
Body weight (kg)	63.51 ± 1.42	0.85 (0.75 ~ 0.92)	< 0.0001

* The p value denotes that each variable correlated with ICW-BIA using Spearman's rank correlation coefficient (R_s) with 95% confidence interval (CI).

multifrequency, and segmental measurement method. SMF-BIA was performed by a well trained nursing staff according to general recommendations [1]. The measurements were performed after 12-hour fasting and within 30 minutes of emptying the urinary bladder. No physical exercise was allowed for 4 hours before the measurement. Eight tactile electrodes were placed on a person in an upright position for the measurement. The feet electrodes are, four stainless steel electrodes. Two are placed on each foot, one on the heel and one on the rear sole. The hand electrodes are constructed from metal foil coated electrodes. The four electrodes are mounted in two plastic handles one on the palm and one on the thumb of each hand. These electrodes are connected to the current and voltage supply of the device. Impedance is then measured through on-off switches regulated by a microprocessor in the SMF-BIA device. By regulation of these switches in appropriate order, the impedances from different body segments can be detected. The measured body segments were left and right hand, trunk, and left and right leg. The multifrequency measurement is conducted by using multiple frequencies at 5, 50, 250, and 500 kHz, thus measuring a set of 20 segmental resistances for one individual. The microprocessor also regulates switching for different frequencies. By virtue of the basic principle developed by Cha K and coworkers [2], TBW and extracellular water (ECW) are separately computed as TBW = $\rho_1 \times (L^2/R_{high})$ and ECW = $\rho_2 \times (L^2/R_{low})$, where R at high frequency (R_{high}) and R at low frequency (R_{low}) represent the function of the resistivity ρ1 and ρ2, respectively; and L is the length of the segmentation. Therefore, ICW volume is calculated as ICW = TBW- ECW. The mean values of two sets of SMF-BIA measurements were used for analysis. To analyze the repeatability of the study, SMF-BIA was performed five times at intervals of 3 minutes in 9 subjects. The mean of the standard deviation and the coefficient of variation of each set of readings were 0.10 and 0.29%, respectively. The procedure was performed in three minutes or less and the ICW volume was automatically calculated from the SMF-BIA with equations installed in the instrument's program [2].

2.3 MLR and GAM constructions

We used the software S-PLUS 6.2 (Insightful, Corp., Seattle, Washington, USA) to construct MLR and GAM. In MLR, the input variables must be of continuous type (age, BH, and BW); accordingly, the variable "gender" is a categorical type that must be deleted from the conventional MLR analysis. Conversely, GAM is described as a more automatic flexible model that may be used to identify and characterize the effects of nonlinear approximation. In approximation

Table 2 Results of ICW volumes by SMF-BIA, Pierson formula, MLR, and GAM

	ICW (L)	p value*
ICW-BIA	21.47 ± 0.61	—
ICW-PSN	23.72 ± 0.77	< 0.0001
ICW-MLR	21.42 ± 0.59	0.94
ICW-GAM	21.47 ± 0.57	0.96

* The p value denotes that each predictive ICW volume was compared with ICW-BIA using Wilcoxon test.

analysis, GAM has the form $E(Y|X1, X_2, \ldots, X_p) = \alpha + f_1(X_1) + f_2(X_2) + \ldots + f_p(X_p)$. As usual $X_1, X_2, \ldots, X_p$ represent predictors and Y is the response; the f_j's are unspecific smooth ("non-parametric") functions. This allows allowing for an alternative distribution for the underlying random variation in addition to the normal distribution. GAM can be applied in any setting in which linear regression is not typically used. These settings include standard continuous regression, categorical or ordered categorical data, count data, survival data, and time series. GAM in S-PLUS 6.0 automatically computes the appropriate transformation for each independent variable to optimize the prediction of the response. Despite the distribution of and type of predictors, all four variables (gender, age, BH, and BW) can be used in the analysis of GAM with Gaussian family and identity link function to predict ICW volume.

MLR and GAM were trained and validated on all subjects using a leave-one-out cross-validation resampling method which was adapted to partition the original dataset and compute an average score over different partitions [3]. One subject was picked out for validation and the model was trained on the remaining 44 subjects. The chosen subject was returned to the training set, the next subject removed for validation and the model was trained on these 44 subjects. The procedure was repeated for all 45 subjects. This technique is useful to enable all the available subjects to be used in the training process and gives a significant validation of the generalizing ability of the trained models. This process avoids possible bias introduced by relying on any one particular division in the testing and training components.

In addition, another anthropometric equation developed by Pierson RN and coworkers [4], was also used to calculate ICW volume (ICW-PSN) as follows: ICW-PSN = (0.470 – 0.0014 × age) × BW in male and ICW = (0.451 – 0.0021 × age) × BW in female.

2.4 Statistical analysis

Data were analyzed using the MedCalc 9.0 (MedCalc Software, Mariakerke, Belgium) and expressed as mean ± standard error. Univariate correlations between each input variable and ICW volume derived from SMF-BIA were analyzed by Spearman's rank correlation coefficient (Rs) with 95% confidence interval (CI). ICW volumes derived from Pierson formula (ICW-PSN), MLR (ICW-MLR), and GAM (ICW-GAM) were compared with BIA-measured ICW volume (ICW-BIA) by using the Wilcoxon test. The statistical association between ICW-BIA and each predictive ICW volume was also expressed in terms of Rs with 95% CI. To test the performance of the prediction, each calculated ICW volume derived from the Pierson formula, MLR, and

Table 3 Spearman's rank correlation coefficient (R_s), folded empirical cumulative distribution plot, root mean square error (RMSE), Passing-Bablok regression for Pierson formula, MLR, and GAM compared with SMF-BIA.

	ICW-PSN	ICW-MLR	ICW-GAM
Spearman's rank correlation coefficient			
R_s	0.93	0.94	0.95
95% CI	0.88 ~ 0.96	0.89 ~ 0.97	0.90 ~ 0.97
Folded empirical cumulative distribution plot			
Median	-2.54	-0.43	-0.13
Lowest value	-5.04	-3.18	-2.13
Highest value	2.23	3.47	2.79
Goodness of fit			
RMSE	2.89	1.54	1.24
Passing-Bablok regression			
Slope	0.78	1.06	1.03
95% CI	0.70 ~ 0.87	0.93 ~ 1.20	0.93 ~ 1.16
Intercept	3.12	-1.68	-0.69
95% CI	0.66 ~ 5.07	-4.55 ~ 1.13	-3.43 ~ 1.36

GAM was compared with SMF-BIA using folded empirical cumulative distribution plot [3, 5], root mean square error (RMSE) [6], and Passing-Bablok regression [7]. The equation used for RMSE is $\sqrt{\sum_{1}^{n}(ICW_{model} - ICW_{BIA})^2 / n}$, where ICW_{model} is the ICW volume predicted by models, ICW_{BIA} is the ICW volume measured by MF-BIA, and n is the sample size.

3. Results

The characteristics of study subjects are presented in Table 1. Their age ranged from 22 to 78 years old and male to female ratio was 0.67. Among these input variables, gender, BH, and BW were strongly correlated with ICW-BIA statistically ($p < 0.0001$). Table 2 shows results of measured ICW volume by SMF-BIA (21.47 ± 0.61 L) and predictive ICW volumes by MLR and GAM. ICW volume derived from the Pierson formula was significantly higher than ICW volume measured by SMF-BIA. Although no statistical difference was found between ICW-BIA and ICW-MLR or ICW-GAM, the ICW volume predicted by GAM was closer to SMF-BIA than to MLR. As shown in Table 3, all estimates of ICW volume significantly correlated with ICW-BIA (R_s = 0.93 to 0.95, $p < 0.001$). GAM had the highest correlation (R_s = 0.95) compared with other methods. In a folded empirical cumulative distribution plot based on SMF-BIA, GAM had the peak (-0.13) centered most closely to zero and had the shortest tails (-2.13 to 2.79) as shown in Table 3 and Figure 1. GAM also had the smallest RMSE (1.24) compared to other methods. Conversely, the Pierson formula had the peak (-2.54) farthest from zero and much larger tails (-5.04 to 2.23), and maximal value of

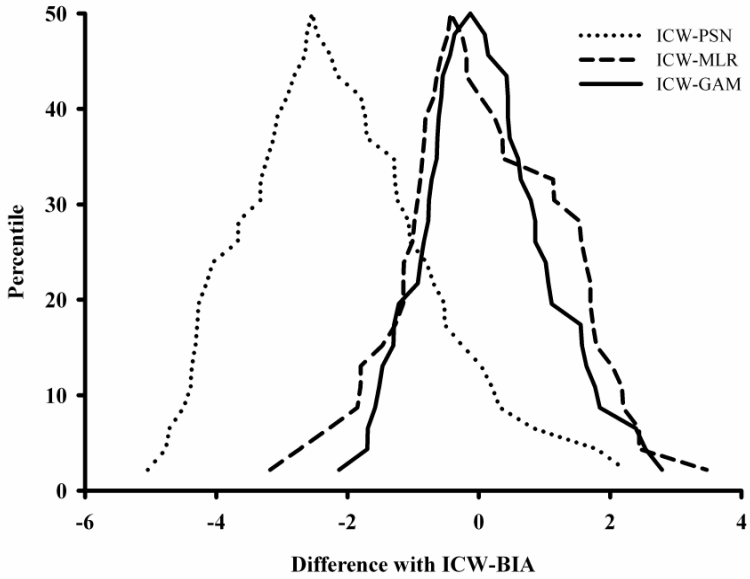
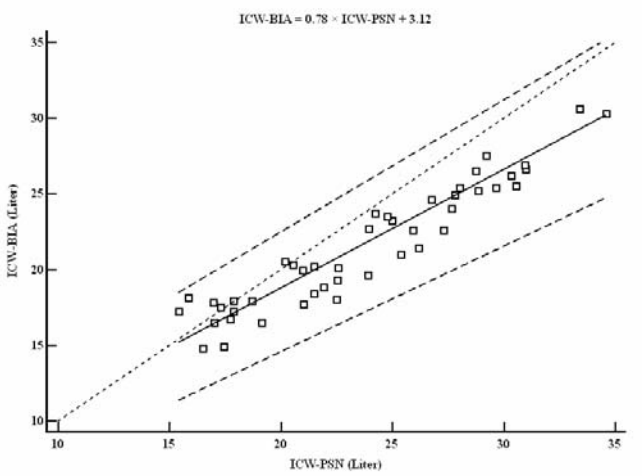


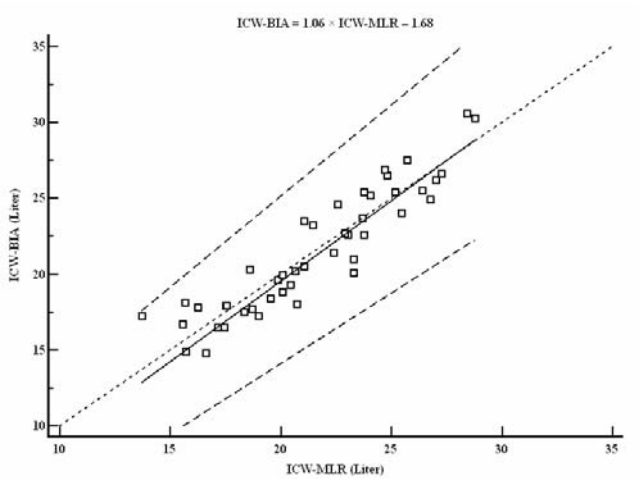
Figure 1 Folded empirical cumulative distribution plot among Pierson formula (ICW-PSN), MLR (ICW-MLR) and GAM (ICW-GAM) based on SMF-BIA (ICW-BIA).

RMSE (2.89) compared with others. Using Passing-Bablok regression analysis for method comparison, the functions were as follows: ICW-BIA = 0.78 × ICW-PSN + 3.12 (Figure 2A), ICW-BIA = 1.06 × ICW-MLR – 1.68 (Figure 2B), and ICW-BIA = 1.03 × ICW-GAM – 0.69 (Figure 2C). Only 95% CI of Passing-Bablok regression for ICW-BIA and ICW-PSN demonstrated the corresponding slope and intercept to be statistically different from one and zero, indicating that Pierson formula and SMF-BIA are not interchangeable with statistically significant deviation from linearity ($p < 0.05$). On the other hand, 95% CIs of MLR and GAM proved the corresponding slopes and intercepts to be not statistically different from one and zero without statistically significant deviation from linearity ($p > 0.05$ for MLR and $p > 0.10$ for GAM), indicating that these two methods are interchangeable with SMF-BIA. However, merely Passing-Bablok regression between ICW-BIA and ICW-GAM with simultaneously narrowest 95% CIs for slope 0.93 to 1.16 and for intercept -3.43 to 1.36 could reflect the best interchangeability for ICW-BIA and ICW-GAM (Table 3).

4. Discussion

SMF-BIA has been used to estimate ICW volume with ease by many clinical researchers. Although SMF-BIA can not measure ICW volume directly as a radiotracer technique, several studies supported its reliability [8-10]. Even though SMF-BIA provides a safe and non-invasive method compared to the radiotracer technique in practical measurement of ICW volume without additional radiation exposure, the equipment and experienced operator are still needed. Therefore, we constructed such an investigation to explore possible models for forecasting ICW volume with data from anthropometric data without using radiotracers or SMF-BIA. Our GAM proved to have better performance in predicting ICW volume than the conventional algebraic equations, either Pierson formula or MLR. ICW volume estimation derived





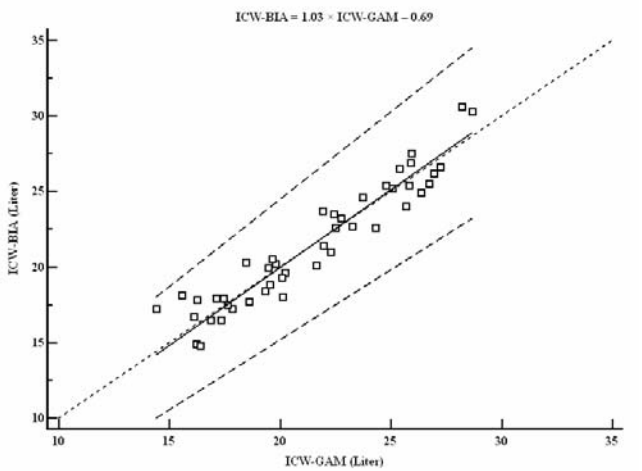


Figure 2 Passing-Bablok regression shows a scatter diagram with regression line (solid line), the 95% confidence interval for the regression line (dashed lines), and identity line (X = Y, dotted line). (A) ICW-PSN vs. ICW-BIA, (B) ICW-MLR vs. ICW-BIA, (C) ICW-GAM vs. ICW-BIA.

from Pierson formula was significantly higher than measured ICW volume, but the difference was not significant from MLR and GAM predictions. Although all three methods significantly correlated with ICW volume measured by SMF-BIA, Pierson formula (Rs = 0.93) and MLR (Rs = 0.94) fitted to a relatively lower correlation than GAM (Rs = 0.95). These probably indicate that conventional algebraic equations based on a linear relationship are not the best model to predict ICW volume in healthy subjects. Even though high correlation of two methods usually means that both methods are linearly related, it does not mean that these two methods agree in statistical analysis. In other words, even though Pierson formula and MLR had relatively lower correlations than GAM, these could not conclude that GAM had the better performance than Pierson formula and MLR.

We adapted a folded empirical cumulative distribution plot to determine the distribution of the differences for performance comparison of the three methods. We chose folded empirical cumulative distribution plot for bias representation due to the following advantages: (1) it is easier to find the central 95% of the data; (2) it is easier to estimate percentiles for large differences greater than 95%; (3) unlike a histogram, the plot shape is not a function of the intervals; (4) comparing different distributions is easier; and (5) the plot is easier to interpret than a standard empirical cumulative distribution plot. With the help of folded empirical cumulative distribution plot, which computes a percentile for each ranked difference between a new method and a reference method, we can display the lack of agreement by presenting the bias as the peak (median) and the difference as the two tails (lowest and highest values). If two methods are unbiased with respect to each other, the peak will be centered over zero with shorter tails in the plot. Of the three methods, GAM had the peak centered most closely to zero with the shortest tails when compared with Pierson formula and MLR in a folded empirical cumulative distribution plot (Figure 1), it indicated that GAM had less bias than Pierson formula and MLR. Furthermore, folded empirical cumulative distribution plot can be used as an index of bias for a new method to compare with a reference method. However, a poor goodness-of-fit can occur in a less biased method. To avoid this pitfall, we used RMSE as a measure of goodness-of-fit for model comparison. If there is more than one model to fit the data, the one with the smaller RMSE value represents the better calibration and higher precision. In terms of RMSE (Table 3), GAM had a smaller RMSE value than Pierson formula and MLR. This confirmed that GAM had the best fit to SMF-BIA. In general, GAM tended to surpass Pierson formula and MLR with lesser bias and higher precision in predicting the ICW volume of healthy subjects in our study.

In traditional statistics, MLR supposes that all predictors are independent with a linear relationship between predictors and response. Also, MLR needs all the input variables to be numerical of continuous variable. Accordingly, the input variable “gender” is dichotomous and can not be selected for MLR analysis. Moreover, we must assume that all input variables are in the condition of normal distribution and independent of each other in MLR analysis. Needless to say, the normal distribution is unrealistic in real world settings and it is dangerous to use these assumptions in biological analysis. In developing a model, a flexible approach is worthy of being favored in that GAM is model independent and pliable in being able to use a combination of continuous and categorical variables based on nonlinear mathematics. Nonlinear phenomenon is essential in medicine and

body constitution research since many variables have an optimal estimate (e.g. body mass index) and will thus correlate with response in a nonlinear pattern. Moreover, there are correlative interactions among predictors (e.g., age and BH, BH and BW) and all predictors do not need to be under the hypothesis of any distributions. Because GAM extends linear regression to allow nonparametric modeling of prediction, it has the characteristics of flexibility without affecting its interpretability. The procedure for fitting is simple and modular, allowing one to select link functions appropriate for the predictors. Furthermore, we used an efficient resampling method, leave-one-out cross validation technique, as our validation step in model assessment and selection. The benefit from accurate prediction of ICW volume by GAM is greater than the difference for adding only one input variable to the models. These particular characteristics make GAM a more robust paradigm for application in the real world. GAM, an advanced flexible model, has been increasingly used successfully to estimate the effects of smoking behavior on lung caner [11], lung cancer rate [12], the relation between amount and type of alcohol and all-cause mortality [13], and serum cholesterol on the mortality of coronary heart disease [14].

In practice at the bedside, there are many anthropometric equations for estimating TBW volume such as the Watson formula [15] and the Hume formula [16]. Thereafter, it is logical to take advantage of anthropometric data as input parameters to build a model in predicting ICW volume. Unlike other equations for TBW volume estimation, there are restricted anthropometry-based equations for ICW volume prediction. We selected Pierson formula for comparison with our MLR and GAM. Pierson formula, a conventional algebraic equation, was constructed by enrolling 58 normal North American (30 males and 28 females) whose gender proportion was not significantly different from ours ($p = 0.33$). The age range of Pierson formula participants was from 19 to 80 years old, also similar to our subjects (22 to 78 years old). In our study, the calculated ICW volume by Pierson formula significantly overestimated the actual measurement of ICW volume by SMF-BIA through direct comparison using non-parametric paired Wilcoxon test; but the difference was not statistically significant from our MLR and GAM forecasting. Although the most unavoidable disagreement is body compositions related to racial difference, other distinctions should be considered. The predictors used in the Pierson formula were confined to three predictors (age, BW, gender). In contrast, we used three predictors (age, BH, and BW) in MLR analysis and for GAM formatted all four fundamental anthropometric predictors (age, gender, BH, BW) into the predictive structure. Correspondingly, the performance is increased powerfully through adding one more variable in GAM. These findings suggest that implementing variables in clinical medicine should not be easily ignored or explained as a completely linear relationship, especially for biological observational studies. In addition, although another anthropometry-based equation developed by Aloia JF and coworkers [17] used the same anthropometric variables (age, BH, and BW) as our MLR, their subjects were all women, and therefore can not be appropriately compared with our study. Another formula also reported by Dittmar M and colleagues [18], was derived not only derived from elderly subjects but also included phase angle and impedance of BIA as some of the predictors. Therefore, it is not simply an anthropometry-based equation for comparison.

Although the study population was relatively

limited in our study, we took advantage of a resampling method, leave-one-out cross-validation procedure, to overcome this problem and achieved the excellent results. We must plan for more subjects to participate in our future investigations. Another potential limitation is the negation of GAM which is thought to be too difficult to operate by physicians. At the present time, with the help of clinician-friendly computer hardware and software, GAM is in fact easy to use automatically as well as more accurate. For any predictive model to be practical in supporting clinical decisions, a most valuable meaning is that only data that are readily and easily available to the clinicians at the time of triage are employed [19]. Before introducing the predictive models into the clinical application for patients, models in predicting ICW volume of healthy subjects should be studied as the baseline. Herein, we developed a flexible model to predict ICW volume to fit the nonlinear biological phenomenon in the real world settings without the assumption of normal distribution.

In conclusion, GAM could be used comparable to the application of SMF-BIA to predict ICW volume in healthy subjects. It is reasonable to use a more accurate method to predict ICW volume. With the help of friendly software, it is worthy and easy to use a flexible model in this evolutional era of information technology without any difficulty. We deeply believe our study using a flexible GAM in predicting ICW volume for healthy subjects will be a basis for future investigations in various diseased states.

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利用彈性模型預測細胞內水量

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摘要

精確預測人體細胞內水量，除了可以評估營養狀態外，也具有許多臨床上的應用。本研究的目的是建構可以預測人體細胞內水量的模型，並與多頻生物電阻分析法作一比較。我們收集四十五位正常人之人體量測資料（年齡、性別、身高、體重），而多頻生物電阻分析法量測出之全身細胞內水量做爲參考值。我們同時評估皮爾森公式、複迴歸線性模型與廣義累進模型預測全身細胞內水量之效能。由廣義累進模型預測之全身細胞內水量（ICW-GAM = 21.47 ± 0.57 L）與多頻生物電阻分析法量測出之全身細胞內水量（ICW-BIA = 21.47 ± 0.61 L）並無統計上的差異（p = 0.96）。與皮爾森公式以及複迴歸線性模型相互比較，廣義累進模型的斯皮爾曼相關係數（0.95）最高，其均方根誤差（1.24）也最小；另外，以經驗累積分佈圖來分析，廣義累進模型的尖峰值（-0.13）最接近零誤差中心，同時雙尾間距最小（-2.13 到 2.79）。佩斯—貝布拉克迴歸統計圖描述多頻生物電阻分析法與廣義累進模型的全身細胞內水量關係式爲：ICW-BIA = 1.03 × ICW-GAM – 0.69，其斜率的 95%信賴區間爲 0.93 到 1.16，截距的 95%信賴區間則爲-3.43 到 1.36，指出廣義累進模型與多頻生物電阻分析法是可以互換的方法（p > 0.10）。廣義累進模型的預測效能比傳統代數公式好，可以是一種預測正常人全身細胞內水量的方法。

關鍵詞：廣義累進模型、複迴歸線性模型、人體量測學、細胞內水分、生物電阻

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