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Bioelectrical impedance analysis values as markers to predict severity in critically ill patients

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Abbreviations

APACHE, Acute Physiology and Chronic Health Evaluation

AUC, areas under the curves

BIA, bioelectrical impedance analysis

ECW, extracellular water

FFM, fat-free mass

FM, fat mass

ICU, intensive care unit

ICW, intracellular water

PhA, phase angle

ROC, receiver operating characteristic

SAPS, Simplified Acute Physiology Score

SOFA, Sequential Organ Failure Assessment

TBW, total body water

Abstract

Purpose: We investigated bioelectrical impedance analysis (BIA)-derived parameters in critically ill patients to evaluate any differences between survivors and nonsurvivors.

Methods: We calculated severity scores for 241 critically ill surgical patients (161 male and 80 female; mean age, 62.9 years) using three severity scoring systems (Acute Physiology and Chronic Health Evaluation II, Sequential Organ Failure Assessment, and Simplified Acute Physiology Score III). Body composition was measured using a portable BIA device for segmental BIA.

Results: Among the BIA values, impedance (odds ratio [OR], 0.99; $P<0.001$), reactance (OR 0.90; $P<0.001$), and phase angle (PhA) (OR, 0.53; $P<0.001$) were highly statistically significant for predicting mortality in univariate and multivariate logistic regression analysis. Comparison of area under the curve (AUC) between severity scoring systems and BIA values showed statistically significant differences between reactance and PhA with all three severity scoring systems. Covariate-adjusted receiver operating characteristic curve analysis showed that compared with severity scoring, all three BIA values (impedance, reactance, and PhA) had higher AUC values.

Conclusions: PhA, impedance, and reactance determined by BIA in critically ill patients were associated with mortality outcomes and revealed stronger predictive power for mortality than severity scoring systems commonly used in an intensive care unit.

Keywords: Bioelectrical impedance, Critical illness, Severity of illness index, Biomarkers

Introduction

Since the condition of critically ill patients can change rapidly, and their vital signs are often unstable, it is difficult to accurately predict mortality or medical outcomes. Therefore, many previous studies attempting to predict the mortality of critically ill patients used severity scoring systems such as Simplified Acute Physiology Score (SAPS), Sequential Organ Failure Assessment (SOFA), or Acute Physiology and Chronic Health Evaluation (APACHE), which use various indicators such as vital signs, blood and urine composition, and urine output. However, because these severity scoring systems often lack accuracy [1-3], efforts are being made to improve them or find more accurate and efficient methods to predict the outcomes.

For Bioelectrical impedance analysis (BIA) analysis, it is generally assumed that the measured body is one cylinder. In contrast, the InBody analyzer uses direct segmental measurement bioelectric impedance analysis (DSM-BIA), a patented technology, to precisely measure the body as 5 separate cylinders, four limbs and the trunk. BIA allows estimation of several factors of human body composition [4,5]. The principle of BIA involves passing a small single- or multiple-frequency alternating current (1–10 μA) through the body and measuring the resulting impedance composed of resistance, capacitive reactance, and the phase angle (PhA). As the body's electrical conductivity depends on its composition (fat and water content), the total body water (TBW), as well as the intra- and extracellular water content (ICW and ECW, respectively) can be estimated. PhA represents the phase difference between voltage and current and is related to the number of healthy cells in the body. Experimental results further allow calculation of fat mass (FM), fat-free mass (FFM), and cell mass by using a regression equation based on measuring values. Furthermore, it is possible to determine the water content and muscle mass for specific body parts such as arms, legs, and the trunk.

As a noninvasive method, BIA is widely used in clinical settings because it provides a convenient tool to easily and quickly examine body composition at a patient's bedside [4-7]. In particular, the PhA is a useful indicator of nutritional status [8-11], and hence for the patient's overall condition [10-13].

BIA studies on critically ill patients are rare due to the concern that their severely imbalanced state of body fluids might affect BIA results [14,15]. However, some recent studies suggested the possibility of evaluating nutritional status and predicting mortality of critically ill patients using segmental BIA [7,16-20].

In the present study, we intended to gain further insight into BIA of critically ill patients and

investigated the question of whether BIA is a useful tool to predict mortality of critically ill patients. For this purpose, we compared BIA data with the popular severity scoring systems SAPS III, SOFA, and APACHE II, which are commonly employed for this prediction [1-3].

Materials and methods

This was a prospective, open-label, observational study.

Subjects

This study was conducted from January 12 to August 3, 2015, in the surgical intensive care unit (ICU) of Ajou University Hospital, Suwon, Korea. A total of 241 critically ill surgical patients (161 male and 80 female, mean age 62.9 ± 13.1 years) over 18 years old were enrolled. Pregnant or brain dead patients were excluded. BIA analysis was performed for all patients regardless of whether they were on diet or fasting, had limb edema, anasarca, sepsis, shock, or undergoing renal replacement therapy. This study was performed after obtaining the approval of the Institutional Review Board (IRB) of Ajou University Hospital (DEV-DE4-15-115). Before inclusion in this study, informed consent was obtained from patients or their next of kin.

Severity scoring systems

SAPS III, SOFA, and APACHE II scores were calculated based on test results or clinical features obtained within 24 hours after admission to the ICU.

BIA measurement

Body composition was measured using a portable BIA device for segmental BIA (InBody S10®, InBody Corp., Seoul, South Korea), using 50-kHz alternating current. The InBody S10 body composition analyzer is designed for patients over 3 years of age who are immobile or who are amputees, with touch-type electrodes or with adhesive-type electrodes and produces results within 2 minutes. With each InBody S10 test, a full-page results sheet is printed detailing the whole-body and segmental (right and left arms and legs and trunk) muscle, fat, and water values such as total body water (TBW), ICW, ECW, ECW/TBW, lean body mass, FM, skeletal muscle mass, and whole-body and segmental PhA, impedance, and reactance at each segment and frequency.

After a patient's admission to the ICU, the measurements were performed twice weekly (Monday and Thursday) in the afternoon between 2 and 4 pm because the researcher who measured BIA was available only at this time. BIA measurements were performed while patients were lying on the bed with their arms and legs spread out. Because it is usually difficult to apply touch-type electrodes to ICU patients due to intravascular lines and dressing covering these lines, we used adhesive-type electrodes. Eight adhesive electrodes were used: one on the most distal part of the third metacarpal bone of each hand, one on each wrist, one on the most distal part of the second metatarsal bone in each foot, and one on the central part of each ankle. In contrast with other BIA devices used for patients who are standing, the InBody S10 cannot measure height and body weight while the patient is lying down. Before pressing the measurement button, manual input of patient information such as age, height, and weight is needed. We used the actual body weight of each patient which was measured by scale in the ICU bed on their exam date. To prevent any errors caused by improper patient postures or inappropriate attachment of the electrodes, photographs were taken and reviewed by co-investigators.

Nutritional assessment

Nutritional assessment was performed for patients with a medium or high risk of malnutrition. Risk factors at the time of admission included 1) unexpected weight loss during the past month; 2) dysphagia; 3) starvation for more than 3 days; 4) anorexia for more than 2 weeks; 5) tube feeding; 6) human immunodeficiency virus infection, chronic kidney disease, liver cirrhosis, hepatic encephalopathy, congenital metabolic disease, sores, multiple trauma, burns on more than 10% of the body surface; g) old age; h) extremely low body mass index; and i) abnormal serum albumin level. Depending on the result of the nutritional assessment, patients were categorized as either well-nourished or malnourished.

Statistical analysis

The first BIA measurement values from patients admitted to the ICU were used for comparisons with severity scores. All continuous data are expressed as the arithmetic mean values ± standard deviation; other data are reported as number (percentage). The normality of each variable was tested using the Kolmogorov–Smirnov test. Student's t-tests were used for comparisons between survivors

and nonsurvivors. Univariate logistic regression analysis with a forward stepwise approach and multivariate logistic regression analysis were performed to investigate correlations of BIA data and severity scores with respect to their ability to predict mortality. Receiver operating characteristic (ROC) curves were generated and areas under the curves (AUCs) calculated.

ROC curves and AUCs were compared using the DeLong method [21]. *P*-values of <0.05 were considered statistically significant.

All of the statistical analysis was performed using R software version 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics are shown in Table 1. Height and weight were 164.4 ± 8.9 cm (range, 140–186 cm) and 64.7 ± 14.7 kg (range, 33–135 kg), respectively. The most common cause of admission was abdominal surgery due to malignant tumors (23.2%), followed by open-heart surgery (17.4%). Malnourished patients accounted for 17.0%, and patients with a shock status needing vasopressors accounted for 60.6%. In-hospital mortality was 19.9%.

The mean time interval from ICU admission to the BIA measurement used for this analysis was 2.3 ± 1.8 days (range, 0–5 days). A comparative analysis was performed between the severity scores and BIA values for survivors and nonsurvivors. The established scoring systems (SAPS III, SOFA, and APACHE II) showed a statistically significant correlation with the difference between survivors and nonsurvivors (Table 1). Among the BIA values, PhA ($P < 0.001$), impedance ($P < 0.001$), and reactance ($P < 0.001$) were statistically different between the two groups. Although ECW, TBW, ECW/TBW, and FM also showed weak statistical significance, all other BIA data were unrelated to patient mortality.

A univariate logistic regression analysis was performed to assess the predictive power of several characteristics (Table 2). All three severity scores exhibited significant predictive power for mortality. Among the BIA values, impedance (odds ratio [OR], 0.99; $P < 0.001$), reactance (OR 0.90; $P < 0.001$), and PhA (OR, 0.53; $P < 0.001$) were highly statistically significant for predicting mortality, whereas ECW, TBW, ECW/TBW, TBW/FFM, and waist to hip ratio displayed somewhat lower predictive power, similar to the severity scoring systems. The three BIA indicators, PhA, impedance, and capacitive reactance, as well as the three severity scores exhibited a high correlation with mortality in

multivariate logistic regression analysis (using age, sex, and body mass index as parameters; Table 3). Statistical significance was much more pronounced in the case of BIA ($P < 0.001$ for all three indicators). This higher correlation between BIA values (PhA, impedance, and capacitive reactance) and mortality is also reflected in the ROC curves (Fig. 1). The AUCs were higher for BIA values than for the severity scoring systems (Table 4).

According to comparisons of AUCs between severity scoring systems and BIA values, PhA, impedance, and reactance showed statistically significant differences with SAPS III, SOFA, and APACHE II (Table 4). Covariate-adjusted ROC curve analysis showed that compared with severity scores, all three BIA values, impedance, reactance, and PhA, have higher AUC values (Fig. 1).

Discussion

In this study, PhA, impedance, and reactance determined by BIA in critically ill patients were strongly associated with mortality outcomes. Indeed, BIA showed stronger mortality predictive power than the severity scoring systems commonly used in an ICU. The methodology of BIA has been used in the past as a tool to predict patient mortality.[8, 9, 12, 18, 22]One study, comprising 30 critically ill patients under continuous veno-venous hemodialysis, revealed that survivors showed significantly lower TBW, ICW, and ECW compared with nonsurvivors [22]. It was claimed that fluid overload was associated with an increased risk for 90-day mortality in critically ill patients with renal replacement therapy. Similarly, in 66 critically ill patients, Lee et al. [18] found statistically significant differences in ECW/TBW and TBW/FFM between survivors and nonsurvivors. In line with these results, BIA values determined in the present study (ECW, TBW, ECW/TBW, and FM) showed significant correlations with patient mortality, but ICW values were not related to outcomes. Even though we analyzed FFM and FM as comparative parameters between survivors and nonsurvivors, edema or hydration can alter these values; therefore, we cannot confirm whether FM could be a meaningful predictive marker for mortality.

Among all BIA-derived compositional data (body fat and water), ECW/TBW seems to be a reliable parameter with respect to predicting mortality (see Table 1). ECW/TBW represents fluid overload, with high values indicating poor health. The main reason for increased ECW ratios in critically ill patients is edema, which can be caused by acute heart or liver failure. A decrease in ICW (with a concomitant decrease in TBW) can occur in the case of severe malnutrition, old age, or cachexia. All these factors

lead to high ECW/TBW values, thus explaining its close relationship with potential death.

The data directly accessible via BIA measurements (impedance, reactance, and PhA) have an even higher predictive power for patient mortality (see Table 1). As the study of da Silva et al. [20], low PhA values were closely related to mortality after performing BIA in 95 ICU patients, and Lee et al. [18] showed a remarkable difference in PhA between survivors (4.1 ± 1.2) and nonsurvivors (2.9 ± 0.8).

Many previous studies that performed BIA emphasized the importance of the PhA, but none investigated impedance or reactance. However, both quantities proved to be highly correlated with mortality in our investigation. Capacitive reactance was even more strongly correlated with mortality than PhA. This result is likely because the Inbody S10 BIA device used in the present study was designed to calculate the reactance value from measured impedance and PhA values, whereas in other studies, BIA devices are designed to calculate the PhA value from measured impedance and reactance values. This means, in Inbody S-10 device measurement, reactance reflects only the membrane integrity of cells, which can be a strong indicator of a cell's condition, even though the PhA values could be affected by body water composition.

Even though we could obtain data using multiple frequencies (1, 5, 50, 250, and 500 kHz and 1 MHz) with Inbody S10 device, we used only the 50-kHz data for analysis, because until now, many studies [9,11,12,20,23] have reported their study data using the 50-kHz frequency. Furthermore, it was difficult for us to analyze the meaning of data obtained using various frequencies. Further study with multiple-frequency BIA is needed.

A major limitation of this study is that there are many factors that interfere with BIA measurements that are currently not well understood. Fluid status variations such as infusions with large amounts of fluids, peripheral edema, overhydration, which are frequently observed in critically ill patients, can affect the BIA parameters. Body weight measured in the ICU also may not be accurate because of the multiple devices, fluid lines, and drainage systems that may be attached to the patient. Furthermore, we do not know the effect of changes in factors such as ambient air and skin temperature or fever, sweating, nutrition and oral feeding, nutritional status, changes in Na and K content, body mass index, and specific conductance of hospital beds on the BIA measurements. However, we still attempted to find the validity of the BIA technique for critically ill patients.

We also did not perform subgroup analyses according to type of surgery, renal replacement

therapy, shock status, or organ failure status. Patients with massive pleural effusion or ascites were also included, and we did not analyze the difference in these patients.

However, in this study, even though there are many unknown factors affecting BIA, very interestingly, BIA parameters such as impedance, reactance, and PhA showed a definite difference between survivors and nonsurvivors and a strong predictive power for mortality of critically ill patients.

Conclusions

In summary, we showed that impedance, reactance, and PhA determined by BIA in critically ill patients were associated with patient mortality. The raw data obtained (PhA, impedance, and reactance) revealed stronger mortality predictive power than the severity scoring systems commonly used in an ICU (APACHE II, SOFA and SAPS III).

Conflict of Interest: none

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Figure legend

Fig. 1 Multivariate-adjusted ROC curves for BIA data (reactance, impedance, and PhA) and severity scores (APACHE II, SOFA, and SAPS III) adjusted for age, sex, and body mass index. A) ROC curve for impedance and severity scores. B) ROC curves for reactance and severity scores. C) ROC curves for PhA and severity scores.

ROC, receiver operating characteristic; BIA, bioelectrical impedance analysis; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; SAPS III, Simplified Acute Physiology Score III; PhA, phase angle; AUC, area under the curve.

Table 1

Comparison of patient characteristics, BMI, severity scores, and BIA data between survivors and nonsurvivors

Variables	Total (n = 241)	Survivors (n = 193)	Nonsurvivors (n = 48)	*P*-value
Age, years	62.9 ± 13.1	62.4 ± 13.9	62.8 ± 13.5	0.885
Sex				
Male	161 (66.8%)	123 (63.7%)	38 (79.2%)	0.059
Female	80 (33.2%)	70 (36.3%)	10 (20.8%)	
BMI, kg/m^2	23.9 ± 5.0	23.9 ± 5.1	23.8 ± 4.2	0.908
Patient category				
Abdominal surgery (malignancy)	56 (23.2%)	46 (23.8%)	10 (20.8%)	
Open heart surgery	42 (17.4%)	34 (17.6%)	8 (16.7%)	
Orthopedic surgery	34 (14.1%)	33 (17.1%)	1 (2.1%)	0.305
Aortic problem	26 (10.8%)	20 (10.4%)	6 (12.5%)	
Liver transplantation	26 (10.8%)	22 (11.4%)	4 (8.3%)	
Abdominal surgery (benign disease)	24 (10.0%)	18 (9.3%)	6 (12.5%)	
Lung surgery	19 (7.9%)	17 (8.8%)	2 (4.2%)	
Others	14 (5.8%)	8 (4.1%)	6 (12.5%)	
Shock (vasopressor use)				
Yes	146 (60.6%)	108 (56.0%)	38 (79.2%)	0.028
No	95 (39.4%)	85 (44.0%)	10 (20.8%)	

Mechanical ventilation				
Yes	164 (68.0%)	67 (32.7%)	12 (25.0%)	0.234
No	77 (32.0%)	126 (65.3%)	36 (75.0%)	
Nutritional status				
Well-nourished	200 (83.0%)	163 (84.5%)	37 (77.1%)	0.281
Malnourished	41 (17.0%)	30 (15.5%)	11 (22.9%)	
Severity scores, points				
SAPS III	44.2 ± 17.0	42.9 ± 17.1	49.3 ± 15.5	0.019
SOFA	6.8 ± 3.6	6.4 ± 3.5	8.1 ± 3.7	0.004
APACHE II	16.2 ± 7.2	15.7 ± 7.2	18.5 ± 7.0	0.016
Clinical outcome, days				
Length of stay in ICU	19.6 ± 18.4	19.6 ± 18.4	19.6 ± 18.4	0.149
Length of stay in hospital	25.0 ± 31.7	20.0 ± 18.9	18.0 ± 16.3	0.142
Duration of MV (n = 164)	12.3 ± 22.8	12.2 ± 24.0	13.2 ± 17.0	0.521
BIA data				
PhA, °	4.0 ± 1.4	4.1 ± 1.3	3.2 ± 1.5	<0.0001
Impedance, Ω	450.2 ± 135.8	472.1 ± 131.3	361.2 ± 117.3	<0.0001
Reactance, Ω	31.4 ± 14.7	34.2 ± 14.2	20.2 ± 11.3	<0.0001
ICW, L	22.7 ± 5.3	22.5 ± 5.2	23.7 ± 5.5	0.161
ECW, L	15.7 ± 3.9	15.3 ± 3.8	17.0 ± 4.1	0.006

TBW, L	38.4 ± 9.0	37.8 ± 8.8	40.7 ± 9.2	0.044
ECW/TBW	0.41 ± 0.02	0.41 ± 0.02	0.42 ± 0.03	0.001
FFM, kg	51.6 ± 11.9	51.0 ± 11.7	54.5 ± 12.2	0.065
FM, kg	13.0 ± 8.4	13.9 ± 8.2	9.3 ± 8.1	0.001
TBW/FFM, L/kg*100	74.2 ± 1.2	74.1 ± 0.9	74.7 ± 1.9	0.053
Protein, kg	9.8 ± 2.3	9.7 ± 2.2	10.2 ± 2.4	0.175
BCM, kg	32.5 ± 7.6	32.2 ± 7.5	33.9 ± 7.9	0.161
BMC, kg	2.8 ± 0.7	2.8 ± 0.6	2.9 ± 1.0	0.505
AMC, cm	26.1 ± 4.3	26.1 ± 4.4	26.2 ± 3.8	0.888
WHR	0.9 ± 0.1	0.9 ± 0.1	0.8 ± 0.2	0.090

Variables are expressed as mean ± standard deviation or number of patients (%).

BMI, body mass index; BIA, bioelectrical impedance analysis; SAPS III, Simplified Acute Physiology Score III; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; MV, mechanical ventilation; PhA, phase angle; ICW, intracellular water; ECW, extracellular water; TBW, total body water; FFM, fat-free mass; FM, fat mass; BCM, body cell mass; BMC, bone mineral content; AMC, arm muscle circumference; WHR waist to hip ratio.

Table 2

Univariate logistic regression analysis of predictors of death during hospitalization

Variable	Odds ratio	95% confidence interval	*P*-value
Age	1.00	0.98–1.03	0.876
Sex	2.13	1.03–4.75	0.050
BMI	1.00	0.93–1.06	0.907
Severity scores			
SAPS III	1.02	1.00–1.04	0.021
SOFA	1.14	1.04–1.26	0.005
APACHE II	1.06	1.01–1.11	0.017
BIA data			
ECW	1.12	1.03–1.21	0.008
TBW	1.04	1.00–1.07	0.046
ECW/TBW	1.44	1.31–1.75	0.001
TBW/FFM	1.53	1.15–2.11	0.005
WHR	0.01	0.00–0.24	0.005
Impedance	0.99	0.99–0.99	<0.001
Reactance	0.90	0.87–0.93	<0.001
PhA	0.53	0.38–0.71	<0.001

BMI, body mass index; SAPS III, Simplified Acute Physiology Score III; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation; BIA, bioelectrical impedance analysis; ECW, extracellular water; TBW, total body water; FFM, fat-free mass; WHR, waist to hip ratio; PhA, phase angle.

Table 3

Adjusted odds ratios of mortalities by severity scores and BIA values in multivariate logistic regression analysis (adjusted for age, sex, and BMI)

Primary independent variable	Odds ratio	95% confidence interval	*P*-value
SAPS III	1.03	1.01–1.05	0.0094
SOFA	1.15	1.05–1.27	0.0043
APACHE II	1.06	1.01–1.11	0.0172
Impedance	0.99	0.99–0.99	<0.0001
Reactance	0.90	0.86–0.93	<0.0001
PhA	0.49	0.35–0.66	<0.0001

BIA, bioelectrical impedance analysis; BMI, body mass index; SAPS III, Simplified Acute Physiology Score III; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation; PhA, phase angle.

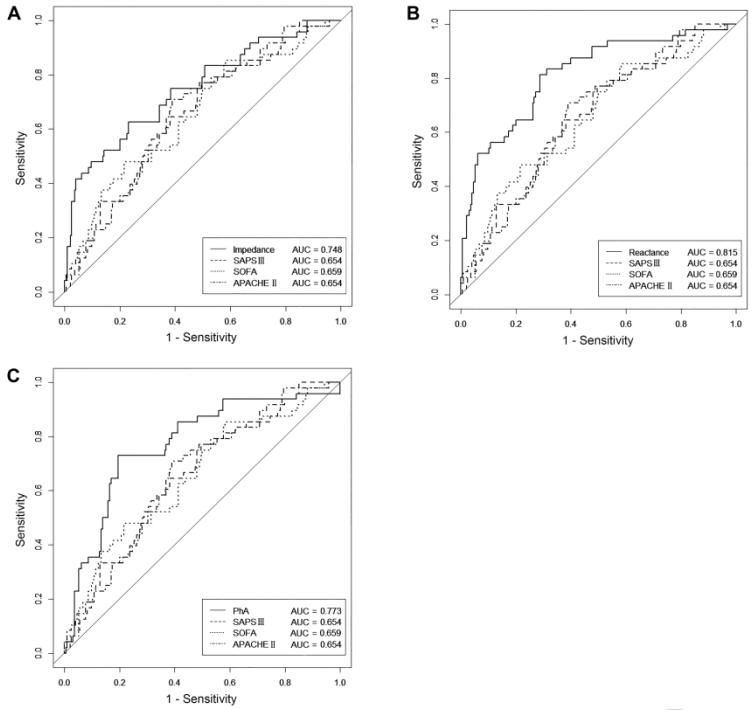
Table 4

Comparison between ROC curves for severity scores and BIA values (adjusted for age, sex, and BMI)

BIA value	AUC, BIA (SD)	Severity score	AUC, severity score (SD)	*P*-value
Impedance	0.748 (0.042)	SAPS III	0.654 (0.042)	0.1173
		SOFA	0.660 (0.042)	0.0953
		APACHE II	0.654 (0.045)	0.1267
Reactance	0.815 (0.036)	SAPS III	0.654 (0.042)	0.0040
		SOFA	0.660 (0.042)	0.0015
		APACHE II	0.654 (0.045)	0.0052
PhA	0.773 (0.039)	SAPS III	0.654 (0.042)	0.0409
		SOFA	0.660 (0.042)	0.0255
		APACHE II	0.654 (0.045)	0.0466

ROC, receiver operating characteristic; BIA, bioelectrical impedance analysis; BMI, body mass index; AUC, areas under the curves; SD, standard deviation; PhA, phase angle; SAPS III, Simplified Acute Physiology Score III; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation.

Figure 1



Highlights of a manuscript entitled "**Bioelectrical impedance analysis values as markers to predict severity in critically ill patients."**

1. Impedance, reactance, and phase angle were associated with mortality outcomes.
2. These were determined using bioelectrical impedance in critically ill patients.
3. They had stronger predictive power for mortality than severity scoring systems.
4. Acute Physiology and Chronic Health Evaluation II, Sequential Organ Failure Assessment, and Simplified Acute Physiology Score III.