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The predictive value of phase angle on long-term outcome after ICU admission.

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Abstract

Introduction: The use of severity of illness scoring systems, including the Acute Physiology and Chronic Health Evaluation (APACHE) III score, has made it possible to compare groups of patients and evaluate treatment strategies. Phase angle, derived from bio-impedance analysis, reflects tissue quality and quantity in which cell mass, membrane integrity and hydration state are represented. We hypothesized that phase angle on ICU admission may serve as a proxy for physical frailty and as such can be used as an additional predictor of long-term mortality after ICU admission.

Methods: A single-center prospective observational cohort study with consecutive patients, admitted to the ICU between June 2018 and June 2019. Demographic data, APACHE III, comorbidity and phase angle in the first 6 hours after ICU admission were collected and the ICU, hospital, and 1-year survival were registered.

Results: Of all 1023 patients, 115 (11%) died within a year after ICU admission. Non-survivors had higher APACHE III scores than survivors (86 [65-119] vs. 55 [46-67], p<0.001). Phase angle was significantly higher in survivors than in non-survivors (5.4 [4.7-6.4] vs. 4.7 [3.9-6.0], p <0.001). Univariate analysis showed an association between mortality and admission type, sepsis, presence of malignancy, APACHE III, and PhA. Multivariate logistic regression analysis using these variables confirmed low PhA to be an independent predictor of 1-year mortality (OR: 1.81; CI: 1.09-2.97; p=0.02), in addition to presence of malignancy (OR: 2.30; CI: 1.31-4.02; p=0.004) and APACHE III score (OR: 1.03; CI: 1.02-1.04; p<0.001)

Conclusion: In this single centre study, low phase angle was independently associated with 1-year all-cause mortality after ICU admission.

ClinicalTrials.gov number: NCT0444976

Introduction

For many decades, clinicians have been in search of relevant markers for outcome of ICU treatment. For this purpose, scoring systems such as the acute physiology and chronic health evaluation (APACHE) score are commonly used [1,2]. However, these scoring systems predominantly predict in-hospital mortality and may be less accurate to acquire a long-term prognosis [3]. This illustrates that not only the severity of disease and the extent of organ failure are associated with mortality after ICU admission [4]. Pre-admission characteristics, including nutritional status and physical frailty, also have been linked to the chance of survival and may hold relevant information with respect to meaningful recovery [5,6].

Yet, objective assessment of premorbid health status may be challenging. In the acute setting, critical information is often missing and evaluation of nutritional status and frailty can be troublesome. An alternative way to obtain information about a patients underlying physical state is by measuring bioelectrical impedance analysis (BIA)-derived phase angle [7]. Previous studies have linked BIA-derived markers to outcome in many disease states [8,9]. Similarly, in patients admitted to the ICU, an association is found between phase angle and short-term mortality [10–13]. Although of relevance, short-term mortality does not reflect the long-lasting impact of critical illness nor the substantial additional mortality within the first year(s). In the present study, we questioned whether BIA-derived phase angle is associated with 1-year mortality after ICU admission.

Methods

Study design

This study was a single-center prospective observational cohort, performed in a 20-bed, closed format mixed ICU. All patients admitted to the ICU between June 1st 2018 and June 1st 2019 were included, with the exception of patients under the age of 18, patients who stayed less than 6 hours in the ICU, and patients who were readmitted. A local medical ethical committee determined this study was eligible to be assessed as a nWMO-research project (Regional Review Committee Patient-related Research, Medical Centre Leeuwarden, nWMO 32, July 12th, 2018). This study has been performed in accordance with the ethical standard laid down in the Declaration of Helsinki and its later amendments. The need for informed consent was waived under the condition that no extra interventions other than standard care were performed.

Data collection

Data were extracted from the electronic hospital information system (EPIC Systems, Wisconsin, USA). Collected parameters included demographic data, reason for admission (acute or elective, surgical or medical), body mass index (BMI), comorbidities (presence of sepsis and active malignant disease), baseline laboratory measurements (C-reactive protein, albumin, and creatinine), the APACHE) III score over the first 24 hours of ICU admission, length of stay at ICU and hospital, ICU and hospital survival, and survival after 3, 6 and 12 months.

Bio-impedance analysis

In line with standard care protocol, BIA-measurements were performed preferably within hours after ICU admission and no later than 24 hours after ICU admission. To perform BIA, two electrodes were placed on the wrist and dorsal site of the hand and on the ipsilateral ankle and forefoot with a distance of at least 5 cm between the electrodes (Biatrodes, Akern Srl, Italy). An alternating current (400 mV and 50-kHz) was sent between the electrodes and the resistance (R), reactance (Xc), and phase angle (PhA) were measured (BIA 101 Anniversary Sport Edition analyzer, Akern Srl, Italy). BIA is based on the electrical principle that the body is a circuit with a given R and Xc. R reflects the opposition of current flow through intracellular and extracellular solution and Xc reflects the capacitance of the cells to store energy [14]. PhA is a ratio of whole-body cellular health and integrity that can be derived from R and Xc as the arc tangent of Xc/R and represents the difference between voltage and current. BIA-derived measurements can vary based on factors like sex, age, and body composition. In addition, changes in body hydration among other alterations in physical status during ICU admission, can alter cellular resistance and therefore PhA [15]

In this study, baseline PhA was used to assess whole body cellular health as a marker for malnutrition and physical frailty. PhA values were compared to previously established cut-off values based on a healthy and well-fed control population ((PhA ≥5 and ≤7 degrees) [16,17]. For men, a PhA beneath 5 and for women a PhA beneath 4.6˚ is considered to reflect an impaired health or malnourishment.

Statistical analysis

The primary aim of this study was to assess all-cause one-year mortality after critical illness. Data are presented as median and interquartile range [IQR], according to their distribution. For comparison between groups, an independent sample t-test was used in case of normal distribution or a Mann-Whitney test in case of non-normal distribution. A chi square test was performed in case of categorical variables. A multivariate logistic regression analysis was performed (backward Wald). In addition, a receiver-operating characteristic

(ROC) curve analysis was used to identify an optimal cut-off value for PhA as a predictor of mortality. All variables with a p-value < 0.25 in the univariate analysis were included. A two-sided p-value of <0.05 was considered statistically significant. Statistical analyses were performed using The Statistical Package for the Social Sciences 24.0 (IBM, New York, NY, USA).

Results

Of the 1413 patients admitted during the study period, we included a total of 1023 patients in our analysis. A total of 390 patients were not included due to exclusion criteria (132) or absence of BIA measurements (258). At admission, patients were 68 [60-74] years old, 67% was male, and BMI was 26.3 [23.9-29.4] (Table 1). Sixty-three percent of the patients were admitted after elective surgery. The median value of phase angle was 5.4 [4.6-6.4]. There was no difference in baseline phase angle between patients who were admitted after elective surgery or after acute admissions (p = 0.233).

Table 1. Baseline and 1-year survival

	All	**Survivors**	**Non-survivors**	**p-value**
Number of patients, n	1023	908	115	
Sex, male, n (%)	686 (67)	609 (67)	77 (67)	.980
Age, years	68 [60-74]	67 [60-74]	70 [63-75]	.091
BMI, kg/m^2	26 [24-29]	26 [24-29]	27 [24-29]	.504
Admission type, n (%)				
Elective	648 (63)	615 (68)	33 (29)	< .001
Acute	374 (37)	292 (32)	82 (71)	
Sepsis, n (%)	79 (8)	56 (6)	23 (20)	< .001
Malignancy, n (%)	130 (13)	97 (11)	33 (29)	< .001
Mechanical ventilation, n (%)	853 (83)	758 (84)	95 (83)	.793
Laboratory tests,				
CRP, mg/l	16 [4-100]	13 [3-81]	49 [6-153]	.002
Creatinine,	85 [70-104]	84 [69-101]	106 [72-153]	< .001
µmol/l	26 [21-31]	27 [21-32]	24 [19-29]	.004
Albumin, g/l				
APACHE III	57 [47-71]	55 [46-67]	86 [65-119]	< .001
Resistance, Ω	449 [385-508]	449 [388-508]	444 [360-519]	.521
Reactance, Ω	42 [42-51]	43 [37-51]	38 [28-48]	< .001
Phase Angle, °	5.4 [4.6-6.4]	5.4 [4.7-6.4]	4.7 [3.9-6.0]	< .001
Phase Angle < 4.6, n (%)	268 (26)	211(23)	57 (49)	< .001

Abbreviations: BMI, Body Mass Index; CRP, C-reactive protein; APACHE, Acute Physiology and Chronic Health Evaluation; BIA, Bio Impedance Analysis.
Results are displayed as: number (percentage) or as median [interquartile range].
P-value represent difference between survivors compared with non-survivors

Of all patients, 115 (11%) died within a year after admission to the ICU. Non-survivors had APACHE III (86 [65-119] vs. 55 [46-67], p<0.001) scores than survivors, indicating a

higher severity of illness. PhA in patients that survived after 1 year was significantly higher in survivors than in non-survivors (5.4 [4.7-6.4] vs. 4.7 [3.9-6.0], p <0.001). ROC curve analysis determined the optimal phase angle cut-off value (Youden index), for the prediction of 1-year mortality was 4.6˚ (Figure 1). The area under the curve was 0.63 (95% confidence interval: 0.58-0.70) with a sensitivity of 80% and specificity of 49%.

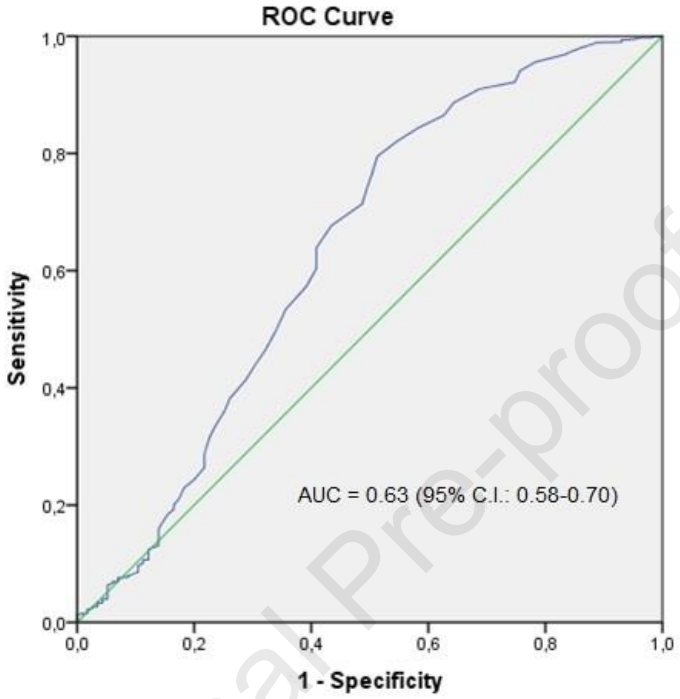


Figure 1: ROC curve of Phase angle

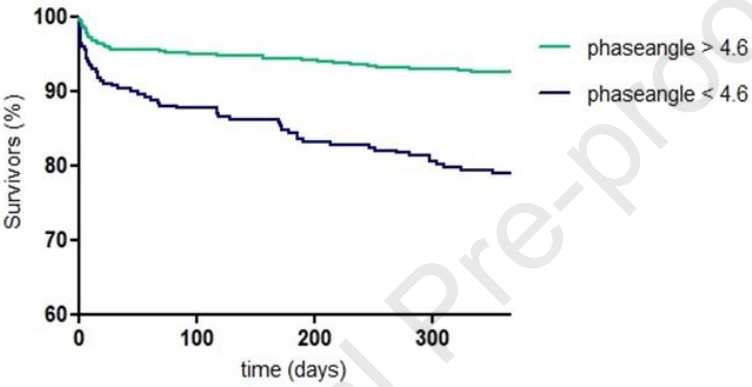
Univariate analysis showed an association between mortality and admission type, sepsis, presence of malignancy, APACHE III, and low PhA. Multivariate logistic regression analysis using these variables confirmed low PhA to be an independent predictor of 1-year mortality (OR: 1.81; CI: 1.09-2.97; p = 0.02), in addition to the presence of malignancy (OR:2.30; CI:1.31-4.02; p=0.004) and APACHE III score (OR:1.03; CI:1.02-1.04; p<0.001) (Table 2).

Table 2: Univariate and multivariate analysis of 1-year mortality

Risk factor	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Low PhA (<4.6 degrees)	3.242 (2.180-4.820)	<0.001	1.81 (1.09-2.97)	0.020
APACHE III	1.045 (1.037-1.053)	<0.001	1.03 (1.02-1.04)	<0.001
Admission type: acute	5.251 (3,425-8,052)	<0.001		
Presence of sepsis	3.799 (2.234-6.460)	<0.001		
Presence of malignancy	3.361 (2.131-5.300)	<0.001	2.30 (1.31-4.02)	0.004
CRP at admission	1.003 (1.001-1.005)	0.002		
Serum albumin at admission	0.951 (0.920-0.983)	0.003		

OR, odds ratio; CI, confidence interval

Using the previously identified optimal cut-off PhA value, a Kaplan Meier curve for 1-year survival of the group with low PhA and the high PhA group indicated all-cause 1-year mortality was significantly higher in patients with a low PhA ($p < 0.001$, Figure 2). Using a Cox proportional hazard model corrected for APACHE III score, PhA remained a significant predictor of survival (Hazard ratio 1.850, CI: 1.269-2.699, $p = 0.001$).



	t= 0	t = 90	t = 180	t = 270	t = 365
Phaseangle > 4.6 (n)	755	717	712	702	698
Phaseangle < 4.6 (n)	268	234	225	218	210

Figure 2: Kaplan Meier curve of 1-year survival of patients with low and higher PhA.

Discussion

In our study BIA-derived PhA was an independent predictor of one-year mortality after ICU admission in a mixed population of medical and surgical, acute and elective ICU patients. In several studies, a predictive value of PhA was reported after 28 to 90 days follow-up, but to our knowledge this is the first study with a follow up of one year [10–12].

In our population, we confirmed 4.6 degrees as an optimal cut-off value for PhA in relation to long term mortality after ICU admission. This was in line with previous observations by Stapel et. al (2018), with an optimal cut-off value of 4.8 degrees in ICU patients 90 days after ICU admission. In many disease states, including cancer, renal failure, and chronic neurological diseases a lower PhA is associated with decreased survival [9]. It is conceivable that in specific ICU-patient groups tailored cut-off values of PhA can be identified, as suggested in a study with COVID-19 patients, where a cut-off value 3.95 was found [11].

To interpret the value of PhA at the time of ICU admission some considerations should be made. BIA-derived PhA assigns a value to body composition, in which a lower value reflects less muscle tissue, more extracellular fluids and/or diminished cellular function. There is debate whether PhA can be used to determine pure disease-related malnutrition, and there is overlap as many clinical conditions, including underlying malignancies, lead to a higher protein catabolic rate. In a general population, sex, age and BMI are important determinants of phase angle [16]. With increasing age, PhA decreases as the amount of muscle tissue decreases. A higher BMI is associated with a higher PhA, albeit within the normal range. However, in this study there were no differences in sex, age and BMI between survivors and non-survivors.

In general, an AUC between 0.6 and 0.7 is considered fair, but not an all-defining silver bullet. Comparison of the odds between the independent risk factors should be done with caution. The presented odds ratios for PhA are per grade or per point in case of APACHE III score, but dichotomous with respect to the presence of malignancy. Another important factor in the interpretation of the PhA is the hydration status, since fluid overload leads to a decrease in resistance and a lower value of PhA. Vice versa, in patients with dehydration, resistance will increase which results in a higher phase angle [15]. This limits the ability for sequential PhA measurements during ICU admission, when fast shifts during fluid resuscitation and de-escalation are to be expected.

To summarize, on ICU admission BIA-derived PhA may provide additional objective and easy-to-obtain information on a patient's body composition and, as a proxy for physical frailty, serve as an indicator for his/her ability for long term recovery. Further research is needed to determine whether PhA measurement is indeed an acceptable proxy for nutritional status or physical frailty. Furthermore, the potential for PhA monitoring in the post-ICU phase in the guidance of rehabilitation interventions needs further elucidation. The main limitation of the study is the fact that in about one-third of admissions during the study period PhA measurement was not performed, creating potential bias. Post-hoc analysis revealed that characteristics of this group were comparable in all major determinants of PhA (data not shown), and therefore probably did not influence the outcome of the study.

In conclusion, in this single center study PhA was independently associated with 1-year all-cause mortality after ICU admission. However, more evidence is needed to establish the added clinical value of bioimpedance measurements prior to and after ICU admission.

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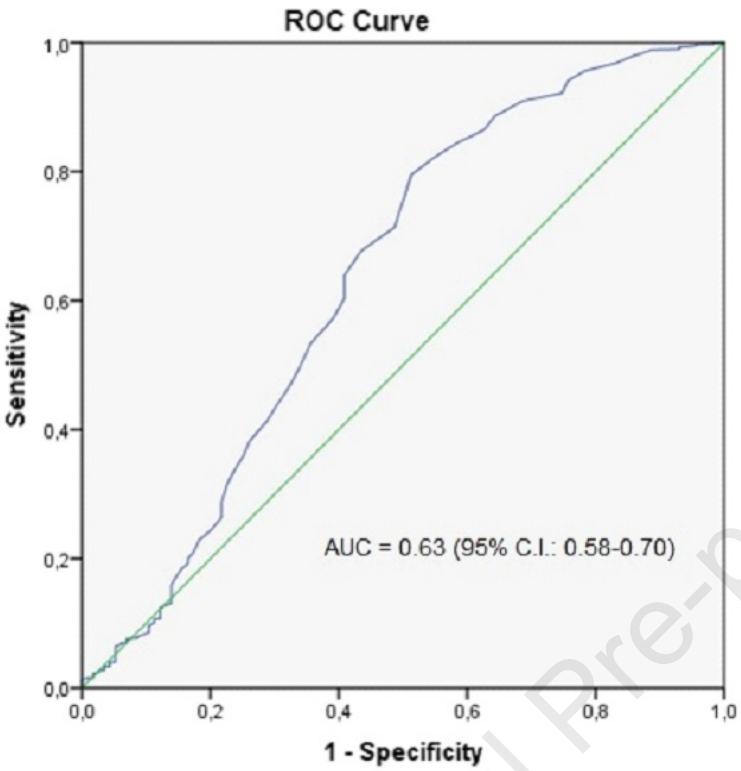

Figure 1. ROC curve of Phase angle

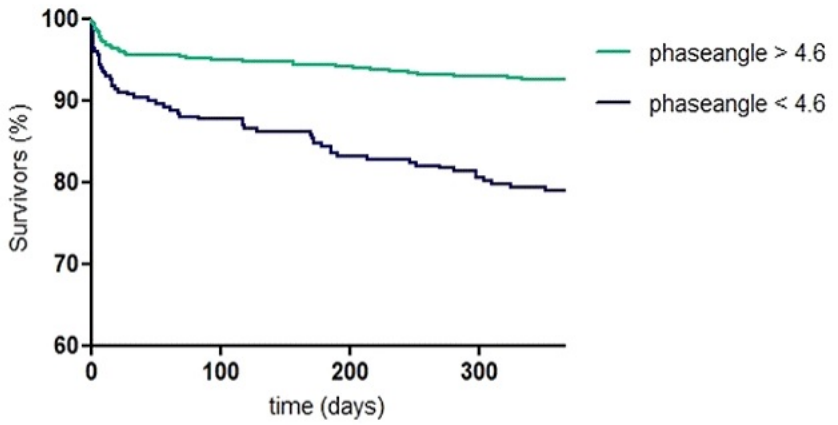

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Figure 2. Kaplan Meier curve of Phase angle.