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Fat-free mass at admission predicts 28-day mortality in intensive care unit patients: the international prospective observational study PHASE ANGLE PROJECT

<u>Running title:</u> The PHASE ANGLE PROJECT

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ABSTRACT

Purpose: Phase angle measured by bioelectrical impedance analysis reflects fat-free mass. Fat-free mass loss relates to worse prognosis in chronic diseases. Primary aim: to determine the association between fat-free mass at intensive care unit admission and 28-day mortality. **Methods:** Design: multicentre prospective observational study in 10 centres in 9 countries. Inclusion criteria: age >18 years, expected length of stay >48 hours, absence of pacemaker, heart defibrillator implant, pregnancy or lactation. Fat-free mass was measured by 50 kHz phase angle at admission. Primary endpoint: 28-day mortality. Statistics: Area under the receiver operating characteristic curve (AUC) assessed 28-day mortality prediction by fat-free mass at admission. Multivariable logistic regression: variables associated with 28-day mortality. **Results:** Out of 3605 screened patients, 931 were analyzed: 61±16 years, male 60%, APACHE II 19±9, body mass index 26±6, day 1 phase angle 4.5±1.9°. Day 1 phase angle was lower in patients who eventually died than in survivors (4.1±2.0 vs 4.6±1.8°, P=0.001). Day 1 phase angle AUC for 28-day mortality: 0.63 [0.58–0.67]. In multivariable analysis, were independently associated with 28-day mortality: age (adjusted odds ratio (aOR) 1.014 [95% confidence interval, 1.002–1.027], P=0.03), day 1 phase angle (0.86 [0.78–0.96], P=0.008), APACHE II (aOR 1.08 [1.06–1.11], P<0.001), surgical patients (aOR 0.51 [0.33–0.79], P=0.002), and admission for other diagnosis (aOR 0.39 [0.21–0.72], P=0.003). A multivariable combined score improved 28-day mortality predictability: AUC=0.79 [0.75–0.82]. **Conclusion:** A low fat-free mass at intensive care unit admission is associated with 28-day mortality. A combined score improves mortality predictability.

INTRODUCTION

Intensive care unit (ICU) patients feature a loss of fat-free mass up to 440 g/day, which is associated with increased morbidity and prolonged recovery [1]. In several clinical conditions, fat-free mass [2] derived from bioelectrical impedance analysis have been associated with worse clinical outcome [3-7]. However, solid data to support this association in ICU patients are lacking. Only a single retrospective study of 51 ICU patients with acute respiratory failure correlated loss of active cell mass with mortality [8]. In a pilot study published in an abstract form performed in 55 ICU patients, we observed that phase angle measured at 5 kHz was significantly related to the Sequential Organ Failure Assessment (SOFA) (r=0.38, P=0.03) [9]. These studies suggest that phase angle, that reflects fat-free mass, may be useful in predicting ICU morbidity and mortality (**Figure 1**).

Bioelectrical impedance analysis is a well validated, non-invasive and relatively inexpensive technique to measure body composition [1]. In the ICU, bioelectrical impedance analysis is frequently described as a non-reliable technique to assess nutritional status through body composition, i.e. fat-free mass or fat mass, because of rapid fluid shifts. This is related to the equations used that have all been validated in clinical situations associated with fluid homeostasis and constant water content. Phase angle is easily, quickly, and repeatedly measured at bedside by bioelectrical impedance analysis. Phase angle is reflecting intracellular status and fat-free mass (**Figure 1**): altered intracellular water to extracellular water distribution is suggested by low phase angle [3].

Phase angle measurement does not require recalled parameters, body weight, and lab tests.

Classic ICU validated severity scores (e.g. Acute Physiology and Chronic Health Evaluation (APACHE), Simplified Acute Physiology Score (SAPS), SOFA) and recent nutritional scores have been developed to foresee the clinical outcome of ICU patients [10]. Most of these scores are time consuming and suffer some degree of discriminative power (i.e. APACHE II and SAPS II are not validated in cardiovascular surgery patients [11, 12]).

We conducted an international multicentre prospective observational study in ICU patients to assess the prognosis value of fat-free mass at admission (day 1) measured by bioelectrical impedance analysis-derived phase angle. The primary aim was to determine the association between day 1 phase angle and 28-day mortality. The secondary aim was to determine the relation between day 1 phase angle and disease severity scores (APACHE II and SAPS II).

METHODS

Study design

The Phase angle Project is an international multicentre prospective observational study involving the intensive care departments and nutrition units of ten centres in nine countries: Geneva (Switzerland), Pelotas (Brazil), Brussels (Belgium), Vilnius (Lithuania), Clermont-Ferrand (France), Ljubljana (Slovenia), Palma de Majorque (Spain), Bydgoszcz (Poland), Zagreb (Croatia), and Rouen (France). The project was coordinated by the Nutrition unit, Geneva University Hospital, Geneva, Switzerland, with RT as the international study coordinator. The research protocol was approved by the Geneva University Hospitals Ethics Committee, then by the Ethical Committee of each participating hospital. The total number of beds among the participatings ICUs was 320, including 70% of medical and 30% of surgical beds.

Patients' recruitment

Each participating centre had to include 100 consecutive patients. This means that during the inclusion period, each centre should include all admitted patients meeting the inclusion criteria until the goal of 100 included patients was reached. For one single patient, the study duration was one month. The overall inclusion period took place from September 1st 2012 and April 30, 2015. The inclusion criteria were: age >18 years, expected length of stay >48 hours, absence of pacemaker or heart defibrillator implant, absence of known pregnancy or lactation, affiliation to an health insurance, and written informed consent by the patient or her/his next of kin in case of inability to

consent. Patients were not eligible if they were readmitted 48 hours after their discharge

to avoid that a single patient was included twice.

Study endpoints

The primary endpoint was 28-day mortality, i.e. mortality during the 28 consecutive days

following ICU admission. If patients were discharged from the hospital or transferred in

another health care centres, the information of 28-day mortality was collected by

examination of medical records, phone call to the hospital department or to the patient's

general physician.

The secondary endpoints were APACHE II and SAPS II collected at day 1. Day 1 was

defined as the day of ICU admission if patients were admitted at or before noon, or as the

day following ICU admission if patients were admitted after noon.

Phase angle measurement by bioelectrical impedance analysis

50 kHz phase angle was measured by bioelectrical impedance analysis in every patient at

day 1 (day 1 phase angle), and repeated at day 5 for patients still hospitalized in the ICU.

After skin cleaning with 70% ethanol, four adhesive electrodes (3M Red Dot T, 3M

Health Care, Borken, Germany) were placed on the dorsal side of the left hand, left wrist,

left foot, and left ankle (**Figure 1**) while the patient was lying supine with hand palms

facing inwards. If the left side was not accessible (e.g. wounds, fracture,…), the right side

was chosen. Phase angle measurement at day 5 was performed with respect to day 1

electrodes position. An electrical current of 0.8 mAmp was produced at 50 KHz by a

generator/analyser (Nutriguard M, DataInput, Gmbh, Darmstadt, Germany) during

approximately two minutes to measure whole-body resistance (R) and reactance (Xc) [1].

Phase angle was calculated according to the following equation: phase angle (degree) =

arctan(Xc/R)*(180/π) (**Figure 1**).

Data collection

Weight and height were measured or obtained by the patient's or their next of kin's

interview the day of phase angle measurement by bioelectrical impedance analysis. Body

mass index was calculated as weight (kg) divided by squared height (m^2). Clinical

information (primary and secondary admission diagnoses, ICU severity scores, outcomes)

was retrieved by each investigator from the hospital electronic medical record. In Geneva

University Hospitals, the ICU dedicated computerised information data management

system (CliniSoft 6.2, General Electric) was used.

Statistics

Sample size calculation

The sample size calculation was based on the main endpoint, the 28-day mortality, the

recruitment capacity of each centre and the estimation of statistical power. Based on other

recent prospective randomized controlled trials [13,14], and statistics from the ICU

department of the Geneva University Hospitals, we expected a 28-day mortality of 15%.

To obtain a area under the receiver operating characteristic (ROC) curve assessing 28-day

mortality prediction by phase angle of 0.85, and given bilateral α and β risks of 5 and

10%, respectively, 1000 patients had to be recruited [15]. We therefore planned to

include 100 patients per centre.

Statistical analysis

Descriptive statistics are expressed as mean ± standard deviation or median and

interquartile range for continuous data, according to their distribution, and number of

patients (percent, %, followed immediately after by the counts for the

numerator/denominator) for categorical data. Receiver Operating Characteristic curves

were used to analyse the association of each variable with 28-day mortality, and to find

the best cut-off associated with 28-day mortality according to the Youden method.

Receiver Operating Characteristic curves are analysed with their area under the curve

(AUC) and its 95% confidence interval. Discriminative power of AUC was determined

according to the following classification: 0.90≤AUC≤1.0, excellent; 0.80≤AUC<0.90,

good; 0.70≤AUC<0.80, fair; 0.60≤AUC<0.70, poor; 0.50≤AUC<0.60, fail [16]. We

analyzed 28-day mortality with the χ2 tests (or Fisher's exact test when appropriate) for

categorical data, and the Student's *t* test (or Mann-Whitney-Wilcoxon test when

appropriate) for continuous data. A multivariable logistic regression adjusted for the

factors with a P-value<0.2 in the univariate analysis was performed with a backward

stepwise elimination process eliminating all variables that did not contribute (P-

value ≥0.05). For continuous variables, the adjusted odd ratio was expressed for 1-point

increase. From this model we computed a risk-score of 28-day mortality. Results are

expressed as adjusted odds ratio and their 95% confidence interval. The risk-score was

used in a Receiver Operating Characteristic curves analysis to assess its discriminative

power towards 28-day mortality. Sensitivity, specificity, positive predictive value and

negative predictive value, and their 95% confidence interval were calculated according to

the Youden method. Statistics were computed with STATA V12 (Stata Corp, College

Station, Texas, USA) and two-sided P-value<0.05 was considered statistically significant.

RESULTS

Patients' selection, characteristics and outcomes

Among 3605 screened patients, 1009 patients were first included according to the inclusion criteria, and after secondary exclusions (8%, 77/1009), 931/3605 patients were analyzed (26% of screened patients) (**Figure 2**). Sixty-four percent (49/77) of secondary exclusions occurred mainly because bioelectrical impedance analysis was not performed at admission. Analyzed patients were included from the 10 participating centres as follow: Geneva (n=170), Ljubljana (n=107), Pelotas (n=103), Brussels (n=100), Vilnius (n=100), Clermont-Ferrand (n=99), Palma de Majorque (n=96), Rouen (n=56), Bydgoszcz (n=51), and Zagreb (n=49). Patients' characteristics and diagnoses at admission are detailed in **Table 1**. Mean day 1 phase angle was 4.5±1.85° (range: 1.24 – 21.0). Day 1 phase angle was measured in 932 patients; one patient was secondly excluded because of aberrant result (day 1 phase angle =0). As expected, day 1 phase angle was lower in older patients, female and patients with lower body mass index (data not shown). SAPS II was collected in 657 patients since it was not collected in routine clinical practice in two centres. Patients' clinical outcomes during follow up are shown in **Table 1**.

Relation between day 1 fat-free mass and 28-day mortality

28-day mortality was 19.3 % (180/931) (range 9.6–38.8%), close to the 15% mortality predicted for the sample size calculation. Day 1 phase angle was lower in non-survivors than in survivors (**Table 1** and **Figure 3A**). This difference failed to reach statistical

significance at day 5 in the 527/931 patients (57%) remaining hospitalized in the ICU.

The area under the receiver operating characteristic curve assessing 28-day mortality

prediction by day 1 phase angle was: 0.63 [95% confidence interval, 0.58–0.67] (**Figure**

3B), indicating a poor discriminative power of day 1 phase angle. 28-day mortality was

higher in patients with day 1 phase angle <3.49 (31%, 86/275) than with Day 1 phase

angle ≥3.49 (14%, 94/656), P<0.001. The areas under the Receiver Operating

Characteristic curve assessing 28-day mortality prediction by APACHE II (n=901) or

SAPS II (n=657) indicated also a poor / fair discriminative power of APACHE II and

SAPS II: 0.69 [95% confidence interval, 0.65–0.73] and 0.72 [95% confidence interval,

0.67–0.77], respectively. Univariate analysis of factors associated with 28-day mortality

is shown in **Table 1**. For the multivariable analysis (**Table 2**), APACHE II and body

mass index were missing in 30 and six patients, respectively, representing 3.9% (36/931),

of missing data. As indicated in **Table 2**, variables significantly associated with increased

28-day mortality in multivariable logistic regression were: day 1 phase angle, APACHE

II, surgical admission diagnosis, admission for another diagnosis that one of those listed,

and age. A multivariable composite risk-score improved 28-day mortality predictability.

The score was determined by multivariable logistic regression and calculated as: risk-

score = – 3.55 [95% confidence interval, –4.67 ; –2.43]– 0.67 [–1.11 ; –0.24] (if surgical

admission diagnosis) + 0.014 [0.002 ; 0.027]* age – 0.146 [–0.254; –0.039]* Day 1 phase

angle + 0.0784 * APACHE II – 0.94 [0.054 ; 0.102] (if admission diagnosis is another

one of those listed)]. For a score ≥0.1716, sensitivity, specificity, positive predictive

value, and negative predictive value, were 77%, 132/172, [95% confidence interval, 70–

83]; 66%, 477/723, [62–69]; 35%, 132/378, [30–40]; and 92%, 477/517, [90–94],

respectively. The area under the Receiver Operating Characteristic curve of this risk-score was: 0.79 [95% confidence interval, 0.75–0.82] (**Figure 4**), improving the discriminative power either values of day 1 phase angle, or APACHE II or SAPS II alone.

Relation between day 1 phase angle and ICU severity scores

There was a correlation between day 1 fat-free mass and ICU severity scores. APACHE II and SAPS II were significantly higher in patients with day 1 phase angle <3.49 than in patients with day 1 phase angle ≥3.49 (APACHE II, 21.8 ± 9.2 vs. 17.7 ± 8.7, P<0.001; SAPS II, 48.0 ± 19.2 vs. 40.5 ± 18.3, P<0.001).

DISCUSSION

In this international multicentre prospective observational study, a low fat-free mass

measured by bioelectrical impedance analysis-derived phase angle at ICU admission was

associated with increased 28-day mortality. A multivariable combined score (including

day 1 phase angle, APACHE II, and other parameters) improves the discriminative power

of 28-day mortality compared to either values of day 1 phase angle, or APACHE II or

SAPS II alone. This study suggests that phase angle could be used as part of prognosis

markers at ICU admission.

In the non-ICU patients, bioelectrical impedance analysis is a well validated and easy-to-

use method to measure at bedside body composition: fat-free mass, fat mass, and total,

intra- and/or extracellular body water, as well as an easy and quick measurement of phase

angle that is a reflect of fat-free mass. A low phase angle is reflecting fat-free mass loss

and cell dysfunction whereas a higher value (>6 in normal subjects [17]) is reflecting

good cell health or nutritional status (**Figure 1**). Low phase angle has been correlated

with a worse disease prognosis in oncology [5, 18-21], human immunodeficiency virus

infection [6], amyotrophic lateral sclerosis [22], geriatric [23], renal dialysis in chronic

renal failure [24], liver cirrhosis [25], acquired immune deficiency syndrome [26], and

gastrointestinal surgical patients [27]. The phase angle cut-off associated with increased

mortality is variable: <2.5° in amyotrophic lateral sclerosis [22], <3.5° in geriatrics [23],

from <1.65 to <5.6° in oncology [18-21], <5.4° in cirrhosis [25], and, in our study,

<3.49° at ICU admission. These differences among cut-offs could be explained by the

lack of homogeneity between these different study populations. The relation of fat-free

mass loss, defined as a low phase angle, with prognosis and illness severity reinforces the interest in using bioelectrical impedance analysis for the clinical management of patients with acute (e.g. ICU) or chronic diseases.

The relationship between fat-free mass and mortality failed to reach statistical significance at day 5. No single explanation is available. This could be related to the reduction of the study sample at day 5 because of early discharge. However, one could have expected a significant relationship between day 5 fat-free mass and mortality. Indeed, at the early phase of ICU stay (i.e. the first 96 hours), critically ill patients feature a loss of fat-free mass up to 440 g/day, which is associated with increased morbidity and prolonged recovery [1]. One could hypothesize that patients with fat-free mass loss at day 5 should more suffer from functional impairment or ICU-acquired weakness [28-30], or could be at increased risk of late mortality (post-28-day).

In our study, APACHE II or SAPS II has a poor/fair discriminative value to predict 28-day mortality. Areas under the receiver operating characteristic curves are much below the values reported in the validation studies of these ICU severity scores [11,12]. This could be explained by the lower sample size or by patients' selection: in the APACHE II validation study, were included only cardiac surgery patients [11], in the SAPS II validation study, were excluded patients with coronary care or cardiac surgery [12], whereas our ICU population was mixed with six percent of cardiac patients. Interestingly, in our study, the mortality predictability of either day 1 phase angle, SAPS II or APACHE II alone was much improved by a multivariable model including day 1 phase angle and APACHE II, among other variables. This indicates that phase angle, a marker of fat-free mass, illness severity and cell health improves mortality predictability of ICU

severity scores. These ICU severity scores are built from clinical and biological data that could not reflect strictly an alteration of cell functions, as does the phase angle. Moreover, phase angle values are dependent on gender, age, and nutritional status: phase angle is lower in female, older, or patients with loss of fat-free mass, i.e. malnourished [17]. Therefore by combining ICU severity scores with a marker of fat-free mass loss, whatever its aetiology (disease severity, chronic diseases, ageing,…), the prognostic value could be improved.

Phase angle is calculated only from two clinical parameters, reactance and resistance, reflecting the electrical properties of body cells. By this fact, phase angle may be less dependent on fluid variations than usual body composition equations. However one could speculate that, in the ICU, rapid fluid shifts, overhydration or dehydration status could contribute to cell damage and therefore be associated with a decreased phase angle. Further studies are needed to better assess the relation between body mass index, body composition including water compartments, and phase angle, in ICU patients. Another applicability of bioelectrical impedance analysis in the ICU could be the bioelectrical impedance vector analysis (BIVA). Indeed Jones et al showed that repeated BIVA hydration measurements could detect fluid accumulation or fluid balance >2 litres in ICU patients [31]. However studies are needed to better define bioelectrical impedance analysis-derived phase angle and BIVA place in the ICU patients' management.

In our study, patients with pacemaker or implantable cardioverter defibrillators were excluded from the study according to the latest European Society for Clinical Nutrition and Metabolism guidelines [2]. However, two studies [32,33] have proven that

bioelectrical impedance analysis can be safely performed in patients equipped with implantable cardioverter defibrillators.

Study limitations. We planned to analyze 1000 patients on a basis of 100 patients per centre, but, due to secondary exclusions, 931 patients were analyzed, and due to 3.9% of missing data, multivariable analysis was performed in 895 patients. Phase angle was shown to be predictive of 28-day mortality in ICU population, known to have rapid fluid shifts. The exact role of these fluid shifts on the observed findings remains to be determined. As previously reported [31], bioelectrical impedance analysis could not be systematically performed in the best conditions: in patients who could not be positioned in a full supine position due to clinical constraints (e.g., those with head injury and intracranial pressure monitoring); on occasion the positioning of the electrodes had to be modified slightly because of the presence of other devices (e.g., intravenous cannulas and soft restraints).

In conclusion, fat-free mass loss, measured at ICU admission by bioelectrical impedance analysis-derived phase angle, is associated with 28-day mortality. Day 1 phase angle, APACHE II, and SAPSII, alone, have a poor discriminative power. A multivariable combined score improves 28-day mortality predictability. Bioelectrical impedance analysis-derived phase angle could be used as a marker of illness severity in the ICU patients. As fat-free mass loss, i.e. low phase angle, defines malnutrition, future studies may be designed to assess whether nutritional interventions targeted to phase angle values could change patients' outcome.

Acknowledgements

Authors' contributions

Ronan Thibault conceived the study, participated in its design, obtained funding, coordinated the study, recruited patients, collected, analyzed and interpreted the data, managed the database, and drafted the manuscript. Anne-Marie Makhlouf recruited patients, collected the data, and managed the database. Aurélien Mulliez performed the statistical analysis. Cristina Gonzalez, Sylvain Dadet, Gintautas Kekstas, Jean-Charles

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1   **Table 1 – Patients' characteristics, diagnoses at intensive care unit admission, and univariate analysis of variables associated**

2   **with 28-day mortality (n=931).** Areas under the receiver operating characteristic curve (AUC) are shown for all variables. Mortality

3   were collected at day 28 even after intensive care unit discharge. The other variables were only assessed during the intensive care unit

4   stay.

	Missing (n)	All n=931	AUC [95% CI]	Alive at 28-DAY n=751	Dead at 28-DAY n=180	OR [95% CI]	*P*-value
Male / female – n (%)	0	561 (60) / 370 (40)	0.50 [0.46 – 0.54]	453 (60) / 298 (40)	108 (60) / 72 (40)	0.99 [0.71 – 1.38]	0.94
Age (year) – mean ± SD	0	61.2 ± 16.3	0.60 [0.55 – 0.64]	60.2 ± 16.4	65.5 ± 15.3	1.02 [1.01 – 1.03]	<0.001
Age <65 / ≥65 years – n (%)	0	463 (50) / 468 (50)	0.59 [0.55 – 0.63]	400 (53) / 351 (47)	63 (35) / 117 (65)	2.12 [1.51 – 2.97]	<0.001
Body mass index – mean ± SD	6	26.4 ± 5.6	0.53 [0.48 – 0.57]	26.5 ± 5.7	25.9 ± 5.2	0.98 [0.95 – 1.01]	0.17
Body mass index (BMI) – n (%)	6		0.53 [0.49 – 0.57]				0.42
<18.5		31 (3)		22 (3)	9 (5)	1.66 [0.74 – 3.75]	0.21
18.5 ≤ BMI <25		409 (44)		329 (44)	80 (45)	Reference	-
25 ≤ BMI < 30		274 (30)		222 (30)	52 (29)	0.95 [0.65 – 1.40]	0.85
30 ≤ BMI < 35		140 (15)		113 (15)	27 (15)	0.97 [0.60 – 1.58]	0.94
≥35		71 (8)		62 (8)	9 (5)	0.59 [0.28 – 1.24]	0.17
Day 1 phase angle (degree) – mean ± SD	0	4.50 ± 1.85	0.63 [0.58 – 0.67]	4.59 ± 1.79	4.10 ± 2.04	0.84 [0.75 – 0.93]	0.001
Day 1 phase angle <3.49 / ≥3.49 – n (%)	0	275 (30) / 656 (70)	0.61 [0.57 – 0.65]	189 (25) / 562 (75)	86 (48) / 94 (52)	2.72 [1.94 – 3.81]	<0.001

APACHE II – mean ± SD	30	18.9 ± 9.0	0.72 [0.67–0.77]	17.8 ± 8.8	23.6 ± 8.6	1.07 [1.05 – 1.09]	<0.001
APACHE II <16 / ≥16[§] – n (%)	30	346 (38) / 555 (62)	0.64 [0.60 – 0.67]	317 (44) / 409 (56)	29 (17) / 146(83)	3.90 [2.55 – 5.97]	<0.001
SAPS II[§] – mean ± SD	274	42.9 ± 19.1	0.72 [0.67 – 0.77]	39.8 ± 17.8	54.8 ± 19.3	1.04 [1.03 – 1.05]	<0.001
SAPS II <46 / ≥46[§] – n (%)	274	391 (60) / 266 (40)	0.68 [0.64 – 0.73]	349 (67) / 171 (33)	42 (31) / 95 (69)	4.62 [3.07 – 6.93]	<0.001
Admission diagnosis – n (%)	0						
Surgical / medical	0	380 (41) / 551 (59)	0.60 [0.57 – 0.64]	336 (45) / 415 (55)	44 (24) / 136 (76)	0.40 [0.28 – 0.58]	<0.001
Diagnosis type							<0.001
Shock (all aetiology)	0	250 (27)	0.59 [0.55 – 0.63]	176 (23)	74 (41)	1.93 [1.15 – 3.24]	0.01
Neurological	0	134 (14)	0.51 [0.48 – 0.53]	110 (15)	24 (13)	Reference	-
Cardiac surgery	0	19 (2)	0.51 [0.50 – 0.52]	18 (2)	1 (1)	0.25 [0.03 – 2.00]	0.19
Trauma	0	34 (4)	0.51 [0.50 – 0.52]	31 (4)	3 (2)	0.44 [0.13 – 1.57]	0.21
Pneumonia	0	54 (6)	0.51 [0.49 – 0.53]	41 (5)	13 (7)	1.45 [0.68 – 3.12]	0.34
Cardiac arrest	0	27 (3)	0.53 [0.51 – 0.55]	14 (2)	13 (7)	4.26 [1.77 – 10.21]	0.001
Respiratory failure	0	154 (17)	0.50 [0.47 – 0.53]	124 (17)	30 (17)	1.11 [0.61 – 2.01]	0.73

Myocardial infarction	0	9 (1)	0.50 [0.49 – 0.50]	8 (1)	1 (1)	0.57 [0.07 – 4.80]	0.61
Acute pancreatitis	0	20 (2)	0.51 [0.50 – 0.52]	19 (3)	1 (1)	0.24 [0.03 – 1.89]	0.18
Liver failure	0	12 (1)	0.51 [0.49 – 0.52]	8 (1)	4 (2)	2.29 [0.64 – 8.23]	0.20
Other	0	218 (23)	0.59 [0.56 – 0.62]	202 (27)	16 (9)	0.36 [0.19 – 0.71]	0.003

5   APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; CI, confidence interval; OR, odds ratio; SAPS,

6   Simplified Acute Physiology Score; SD, standard deviations.

Table 2 – Logistic regression multivariable analysis of factors associated with 28-day mortality (n=895). For continuous variables (age, day 1 phase angle, and APACHE II), the adjusted odds ratio (aOR) are expressed for 1-point increase.

Variables	**aOR**	**95% confidence interval**	*P*-**value**
Age	1.014	1.0016 – 1.0271	0.03
Day 1 phase angle	0.86	0.78 – 0.96	0.008
APACHE II	1.08	1.06 – 1.11	<0.001
Admission diagnosis :			
surgery *vs.* Medicine	0.51	0.33 – 0.79	0.002
Other diagnosis	0.39	0.21 – 0.72	0.003

APACHE, Acute Physiology and Chronic Health Evaluation.

Figures legends

Fig. 1 Measurement of fat-free mass by phase angle derived from bioelectrical impedance analysis: principles and prognostic value. The method of phase angle measurement by bioelectrical impedance analysis is detailed in the "Methods" section
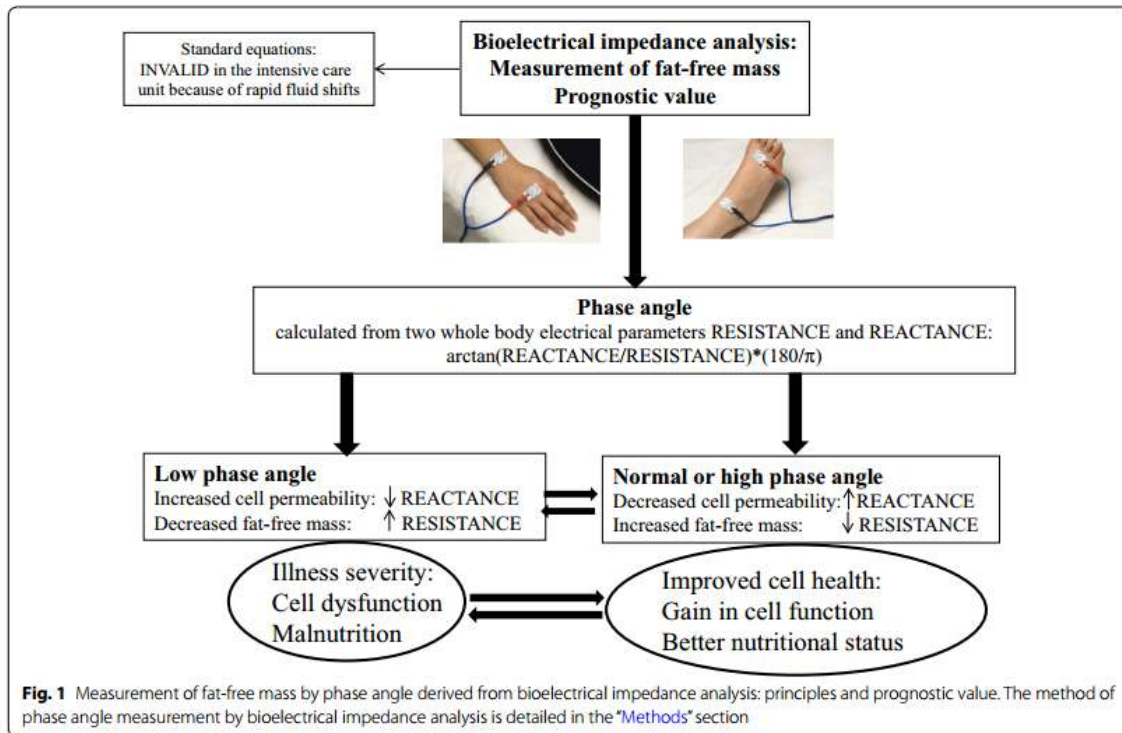
Figure 1 – Measurement of fat-free mass by phase angle derived from bioelectrical impedance analysis: principles and prognostic value. The method of phase angle measurement by bioelectrical impedance analysis is detailed in the dedicated paragraph of the 'methods' section.
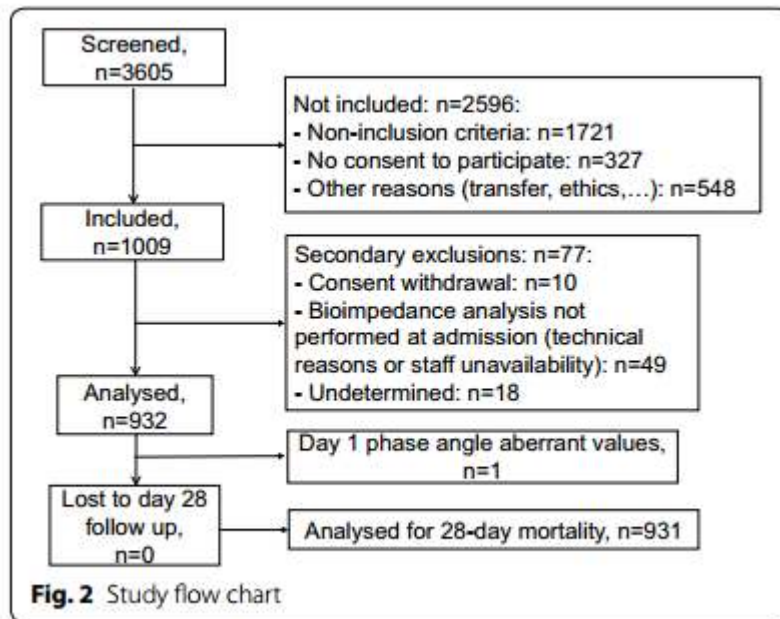
Fig. 2 Study flow chart

Figure 2 - Study flow chart.

Fig. 3 Predictive value of fat-free mass as measured by bioelectrical impedance analysis-derived phase angle at intensive care unit (ICU) admission on 28-day mortality. **a** 28-day mortality according to phase angle values on day 1 (admission) and day 5. Phase angle was measured at admission (day 1) in 932 patients, but the analysis was performed in 931 patients (one patient was excluded due to an aberrant value), and on day 5 in the 540 patients remaining in the ICU at this time. **b** Area under the receiver operating characteristic curve (AUC) assessing 28-day mortality prediction by day 1 phase angle ($n = 931$). A low day 1 phase angle is associated with increased 28-day mortality. AUC = 0.63 [95 % confidence interval (CI) 0.58–0.67]. For a day 1 phase angle of <3.49, sensitivity was 48 % (86/180; 95 % CI 40–55 %), specificity was 75 % (562/751; 95 % CI 72–78 %), positive predictive value was 31 % (86/275; 95 % CI 26–37 %) and negative predictive value was 86 % (562/656; 95 % CI 83–88 %). The day 1 phase angle cutoff associated with 28-day mortality was assessed by the Youden method
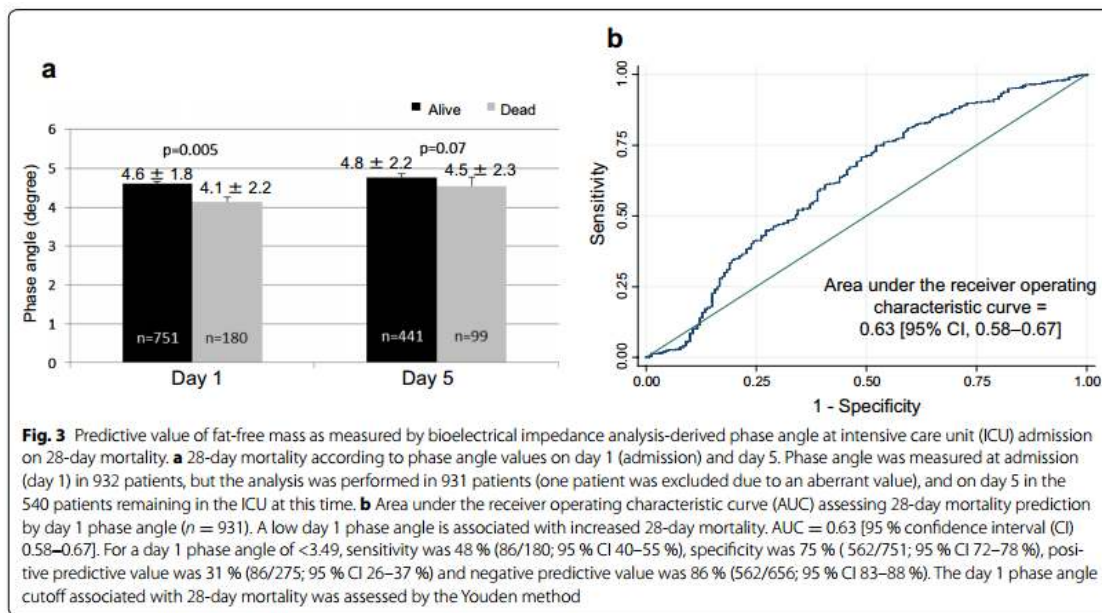
Figure 3 – Predictive value of fat-free mass, measured by bioelectrical impedance analysis-derived phase angle at intensive care unit admission, on 28-day mortality.

(A) 28-day mortality according to phase angle values at day 1 and day 5. Phase angle

was measured at admission (day 1) in 932 patients, but the analysis was performed in 931

patients (one patient was excluded because of an aberrant value), and at day 5 in the 540

patients still in the intensive care unit at this time. **(B) Area under the receiver**

operating characteristic curve (AUC) assessing day-28 mortality prediction by day 1

phase angle (n=931). A low day 1 phase angle is associated with increased 28-day

mortality. AUC=0.63 [95% confidence interval, 0.58–0.67]. For a day 1 phase angle

<3.49, sensitivity, specificity, positive and negative predictive values were respectively:

48%, 86/180, [95% confidence interval, 40–55], 75%, 562/751, [72–78], 31%,

86/275, [26–37], and 86%, 562/656, [83–88]. The day 1 phase angle cut-off associated

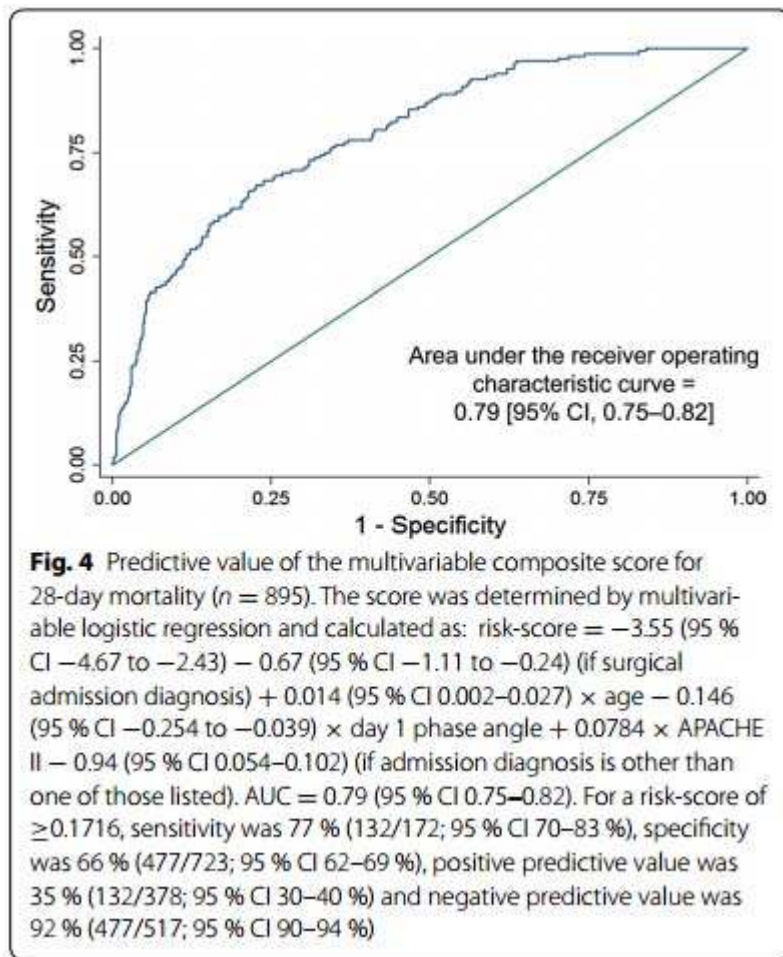with 28-day mortality was assessed by the Youden method.

Fig. 4 Predictive value of the multivariable composite score for 28-day mortality (*n* = 895). The score was determined by multivariable logistic regression and calculated as: risk-score = −3.55 (95 % CI −4.67 to −2.43) − 0.67 (95 % CI −1.11 to −0.24) (if surgical admission diagnosis) + 0.014 (95 % CI 0.002–0.027) × age − 0.146 (95 % CI −0.254 to −0.039) × day 1 phase angle + 0.0784 × APACHE II − 0.94 (95 % CI 0.054–0.102) (if admission diagnosis is other than one of those listed). AUC = 0.79 (95 % CI 0.75–0.82). For a risk-score of ≥0.1716, sensitivity was 77 % (132/172; 95 % CI 70–83 %), specificity was 66 % (477/723; 95 % CI 62–69 %), positive predictive value was 35 % (132/378; 95 % CI 30–40 %) and negative predictive value was 92 % (477/517; 95 % CI 90–94 %)

Figure 4 – Predictive value of the multivariable composite score for 28-day mortality (n=895). The score was determined by multivariable logistic regression and calculated as: risk-score = –3.55 [95% confidence interval, –4.67 ; –2.43]– 0.67 [–1.11 ; –0.24] (if surgical admission diagnosis) + 0.014 [0.002 ; 0.027]* age – 0.146 [–0.254; –0.039]* day 1 phase angle + 0.0784 * APACHE II – 0.94 [0.054 ; 0.102] (if admission diagnosis is another one of those listed)]. Area under the receiver operating characteristic curve = 0.79 [95% confidence interval, 0.75–0.82]. For a score ≥0.1716, sensitivity, specificity, positive and negative predictive values were respectively: 77%, 132/172,

[95% confidence interval, 70–83]; 66%, 477/723, [62–69]; 35%, 132/378, [30–40]; and

92%, 477/517, [90–94].