Clinical Nutrition 38 (2019) 1700–1706

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Bioelectrical impedance analysis (BIA)-derived phase angle (PA) is a practical aid to nutritional assessment in hospital in-patients

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ARTICLE INFO

Article history:
Received 13 March 2018
Accepted 1 August 2018

Keywords:
Bioelectrical impedance
Citrulline
Malnutrition
Nutritional assessment
Phase angle
Transthyretin

SUMMARY

Background: Nutritional status can be difficult to assess. Bioelectrical impedance analysis (BIA)-derived phase angle (PA), and the plasma markers citrulline and transthyretin (pre-albumin) have the potential to assist, but the protocol of fasting and resting for BIA renders the investigation impractical for routine use, especially so in populations at high risk of malnutrition.

Aims: 1 To clarify whether starving and resting are necessary for reliable measurement of PA.
2 To identify whether PA, citrulline and transthyretin correlate with nutritional status.

Methods: Eighty consenting adult in-patients were recruited. Nutritional status was determined by subjective global assessment (SGA) used as gold standard. The Malnutrition Universal Screening Tool (MUST) was used and anthropometric measurements were performed. Serum was analysed for citrulline and transthyretin. PA was measured using Bodystat 4000. The PA was considered to define malnutrition when lower than reference ranges for sex and age, and severe malnutrition if more than 2 integers below the lower limit. Anthropometric measurements were categorised according to WHO reference centiles. Ordinal logistic regression estimated the strength of association of PA, citrulline and transthyretin with SGA. PA values in the different metabolic states were compared using paired t tests.

Results: All 80 subjects completed the BIA and the nutritional assessments in the 3 different states; 14 declined to provide blood samples for the biochemical assays. Malnutrition was identified in 32 cases, severe malnutrition in 14 cases, the remaining 34 cases were deemed not to be malnourished. PA was strongly inversely associated with SGA (Odds Ratio [OR] per unit increase = 0.21, CI 0.12–0.37, $p < 0.001$). PA was not influenced by exercise ($p = 0.134$) or food intake ($p = 0.184$). Transthyretin was inversely associated with malnourished/severely malnourished states (OR = 0.98, 95% CI 0.97–0.99, $p = 0.001$), but had poorer predictive values than PA. There was no significant association between citrulline concentration and SGA (OR = 1.01, 95% CI 0.99–1.04, $p = 0.348$).

Conclusions: The BIA-derived PA reliably identifies malnutrition. It is strongly associated with SGA but requires less skill and experience, and out-performs circulating transthyretin, rendering it a promising and less operator-dependent tool for assessing nutritional status in hospital patients. Our novel demonstration that fasting and bed-rest are unnecessary consolidates that position.

1. Introduction

Malnutrition in hospital inpatients is common, with one study showing that four out of five patients were unable to meet their nutritional demands [1]. Multiple factors are responsible for this including: poor oral intake, increased metabolic demand and bodily stress during illness and recovery. The lack of awareness surrounding the importance of nutrition by the medical team and patient contributes to this problem [2,3]. This is further compounded by a variability in how nutrition is assessed. Most British

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https://doi.org/10.1016/j.clnu.2018.08.003
0261-5614/

in-patients now receive a superficial nutritional status evaluation that uses basic screening questionnaires, which rely heavily on the body mass index (BMI) (as for example with the malnutrition universal screening tool [MUST]) [4,5]. Nutritional screening is recommended by European Society for Clinical Nutrition and Metabolism (ESPEN) which also endorses the Nutritional Risk Screening (NRS), Subjective Global Assessment (SGA) and the Mini Nutritional Assessment [6].

Most of the tools, which encompass and rely upon BMI do not assess nutritional status but rather aim to identify those at risk. Unfortunately, the frequency of fluid retention in hospital patients commonly leads to failures of screening because of the inability of BMI to assess body composition [8,9]. Moreover, there is increasing evidence that assessment of nutritional adequacy depends on the tool or marker used, which in turn affects the apparent prevalence of malnutrition [7].

Subjective Global Assessment (SGA) is a widely endorsed tool for assessing nutritional status; it focuses on the nutritional history and the clinical examination to provide a global impression of the nutritional status of the patient [6]. It is however, time-consuming and requires considerable expertise for full validity, and thereby disqualifies itself from being a global screening tool, while not yet providing a full nutritional assessment. As the prompt and correct identification of malnutrition is essential to improve its management, there is clearly a need for better and less operator-dependent means of nutritional assessment.

Bioelectrical impedance analysis (BIA) is a body composition analysis method, which is non-invasive, portable and inexpensive [10–12]. BIA testing relies on the passage of alternating current through the body and its interactions with cells and tissues. Various readings of resistance and reactance are produced including the phase angle, which takes into account cell membrane integrity as well as body composition.

Wider implementation of BIA is almost certainly limited by the guidelines on its use that oblige the patient to be starved and on bed rest [12,15]. This renders the technique impractical in the clinical setting and introduces an uncomfortable paradox of deliberate short-term starvation in patients likely to be malnourished. Clear evidence that key markers of nutrition and prognosis such as phase angle are affected by food ingestion and exercise is however absent. The situation is further complicated by the variable adherence to intended protocols, even in the literature [13, 14]. It is not known whether the restrictions are truly necessary.

There is currently no biochemical marker of malnutrition used or recommended in mainstream European healthcare. An ideal biomarker would respond to acute changes in nutrition intake, have a short biological half-life, and be unbiased by other disease processes. To date such an entity has been found lacking, as for example in a recent review of markers of nutritional assessment in critical care, which reiterated the need for development of other indicators [16].

Transthyretin (previously widely known as pre-albumin) has properties which should make it particularly suitable as a short-term marker of nutritional status. It has a rapid rate of synthesis that responds to protein intake, and a short half-life of about 3 days [17,18]. In comparison to other serum proteins, it is one of the least affected by liver disease. It is easily quantifiable and relatively inexpensive to determine in a hospital laboratory environment. There are some limitations. Acute alcohol intake can lead to its leakage from damaged hepatocytes, causing an increase in serum transthyretin levels. Medications including prednisolone and progestogens have also been implicated in raising transthyretin levels [17,18]. However, at least one study has demonstrated a significant correlation between transthyretin and SGA in the identification of malnutrition [19].

Citrulline has been identified as a promising marker of enterocyte mass [20,21]. It is a non-protein amino acid whose net production is almost exclusively from enterocytes, with clearance only by the kidney [20]; it is accordingly a reliable marker of enterocyte function [20]. In patients with massive intestinal resection, the citrulline level correlates closely with the length of residual small intestine and with enterocyte mass. Whether Citrulline could represent a useful biomarker of nutritional status is not known.

The present study has explored whether phase angle, transthyretin and citrulline have clinical utility in the nutritional assessment of unselected hospital in-patients.

2. Objectives

1. To determine whether the recommended protocols of starving and resting are necessary for the accurate and reproducible estimation of phase angle by BIA.
2. To determine the associations for PA, citrulline and transthyretin with the diagnosis of malnutrition as defined by subjective global assessment (SGA).
3. To assess the predictive values of PA, citrulline and transthyretin in the diagnosis of malnutrition as defined by SGA.

3. Methodology

3.1. Study design

Cross Sectional Observational Study. *Setting*: Data were collected on two hospital wards at the Norfolk and Norwich University Hospital.

3.2. Participants

Patients were selected following liaison with medical and nursing staff working on the medical wards. Sampling was intended to include a broad demographic of hospital in-patients. Patients were approached one to two days before carrying out the study: information about the study was given by the researcher and inclusion criteria confirmed. Informed written consent was obtained on the morning prior to data collection.

3.3. Inclusion criteria

All patients aged 18 or over who had capacity to consent were potentially eligible for inclusion in the study.

3.4. Exclusion criteria

1 Patients who were metabolically unstable or acutely unwell such that repeated study during a single morning would be precluded.
2 Patients who were pregnant or breastfeeding.
3 Those who were unavailable (for example because of investigations booked for the study morning) making all three phases of study impossible or improbable.
4 Patients who were nil by mouth.
5 Patients in whom bioelectrical impedance testing would be impossible or un-interpretable (e.g. bilateral amputees). Patients with fluid retention or ascites were however fully eligible.

3.5. Process (variables and data measurements)

Height and weight were recorded. Tape and calliper measurements were taken on the non-dominant mid upper arm. The MUST score was recorded. The BIA measurements were performed using the Bodystat Quadscan 4000® BIA machine (Bodystat, Douglas, Isle of Man). Measurements were repeated immediately following a 40 m walk and again 5–10 min following a standard hospital breakfast. A blood sample was taken to measure standard biochemical and haematological parameters including albumin. An additional aliquot of serum was stored at −20 °C for later analysis of transthyretin and citrulline.

For study purposes the gold standard for assessing nutritional status was taken to be the researcher's subjective global assessment (SGA), based on the clinical history and examination. Patients were categorised from their SGA as being nourished, malnourished or severely malnourished. The phase angle was to be considered to indicate malnutrition when readings fell below the lower limit of the reference range for age and sex based on the Barbosa Silva paper cut-off values [22]. Severe malnutrition was deemed to occur with a PA 2 integers below the lower SD of the normal cut-off for PA. This was discussed following expert input from the authors as no current values or cut-offs exist in this regard. It is noted that the reference ranges for PA do not necessarily reflect a UK population as no British data currently exist.

Data were collected and stored electronically.

3.6. Intended sample size and statistical analysis

Eighty adult patients were to be recruited. Patient demographic and clinical characteristics were summarised. PA in the starved and rested state was compared with post-prandial and post-exercise values using paired t tests. PA, plasma Citrulline and Transthyretin levels between SGA groups were compared using one-way ANOVA. Univariate ordinal logistic regression models estimated associations for the outcome, nutritional status, assessed using SGA (with ordinal outcomes nourished [N], malnourished [M] and severely malnourished [S]). The Brant test [23] was used to test the proportional odds constraint that the regression coefficients for the comparison of categories (N versus M and S, and N and M versus S) for each exposure were similar. The proportional odds assumption was violated for plasma transthyretin ($p = 0.009$) but not for phase angle ($p = 0.693$) and citrulline ($p = 0.696$). Therefore the proportional odds model was used to estimate associations for phase angle and plasma citrulline, and a partial proportional odds model was fitted for transthyretin. Analyses were performed with Stata version 13 (StataCorp LP, College Station, Texas, USA) and the stata add-on *gologit2* [24].

3.7. Ethical statement

Ethical approval for the study was granted by The Office for Research Ethics Committees Northern Ireland: REC reference 14/NI/1085.

3.8. Measurements of L-Citrulline

Serum citrulline was measured by liquid chromatography tandem mass spectrometry (LC-MS/MS). Mass spectrometric detection was achieved with a Micromass® Quattro Ultima™ Pt (Manchester, UK), equipped with an electrospray ionisation (ESI) source operating in positive ion mode. Chromatographic separation was achieved using an Agilent 1100 series high performance liquid chromatography (HPLC) system (Cheadle, UK), which delivered water and acetonitrile mobile phases, both containing 0.025% of heptafluoro-butyric acid (HFBA) through a Modus AAC column (Chromatography Direct, Cheshire) at a flow rate of 350 μL/min. L-citrulline was calibrated using standard solutions (Wacko Chemicals GmbH, Neuss, Germany), and L-Citrulline-[$^2H_7$] was used as internal standard (Isosciences, King of Prussia, PA, USA). Prior to LC-MS/MS analysis, 10 μL serum sample was precipitated with 440 μL of 0.1 M hydrochloric acid in methanol containing internal standard. The mixture was vortexed and centrifuged at 10,800 × g for 5 min and 300 μL of supernatant transferred into glass tubes. The supernatant was dried to completeness under a stream of nitrogen at 60 °C. Sample derivatization was carried out with 100 μL of 3 N HCL in n-butanol, and incubated on a heating block at 60 °C for 7 min. Following butylation, the mixture was again dried completely under nitrogen, reconstituted in 250 μL of 12% acetonitrile:water containing 0.025% HFBA, and analysed by LC-MS/MS.

The inter- and intra-assay coefficient of variation (CV) were ≤10.3% between the assay working range of 16.7–833.3 μmol/L. Typical assay recovery is 98–105%.

3.9. Measurements of transthyretin (pre-albumin)

Pre-albumin was measured using immunoturbidimetric assay on a Modular Analytics COBAS c501 analyser (Roche Diagnostics, Burgess Hill, UK). Inter-assay coefficient of variation (CV) was ≤2.2% between 0.55 and 14.6 μmol/L, with lower detection limit of 0.55 μmol/L.

4. Results

Two thirds of those thought potentially eligible were recruited to the study, fulfilling the predetermined size of the study cohort ($n = 80$) (Fig. 1). As intended, the selected patients represented the full adult age range, both genders and a broad range of underlying pathologies (Table 1).

4.1. BIA protocol testing

BIA yielded a clinically representative range of results (2.0–7.9) for the phase angle in our patients. When assessed with regard for age and sex, some 57.5% of PA values fell below the normal range. The overall mean PA in the patients when starved and rested was 4.90 (SD 1.40). This figure did not change after exercise (4.83 [SD 1.33]; $p = 0.134$), nor after exercise and breakfast (4.82 [SD 1.34]; $p = 0.184$).

4.2. PA as a tool for malnutrition

Forty-six patients had a subnormal PA. In 14 of these the value fell at least 2 integers below the lower limit of normal for age and sex. Coincidentally, 46 of the 80 patients also had an abnormal SGA in keeping with malnutrition which was considered severe in 14 (17.5%).

The fasted and rested phase angle (in degrees) for the study sample was 4.9 (SD 4.41), and for the nourished, malnourished and severely malnourished groups respectively was 5.97 (SD 1.20), 4.39 (SD 0.86), and 3.47 (SD 0.88) (Fig. 2). The phase angle was significantly lower in the malnourished ($p < 0.001$) and severely malnourished groups ($p < 0.001$), compared with the nourished group. There was a strong inverse association between PA (on a continuous scale [per degree] and malnutrition as diagnosed by SGA (OR 0.21, CI 0.12–0.37, $p < 0.001$) (Table 2). In no case was severe malnutrition (SGA) missed by PA (100% sensitivity), and in only 2 cases was a low PA predictive of severe malnutrition found in patients who were considered to have normal nutritional status on SGA (94% specificity).

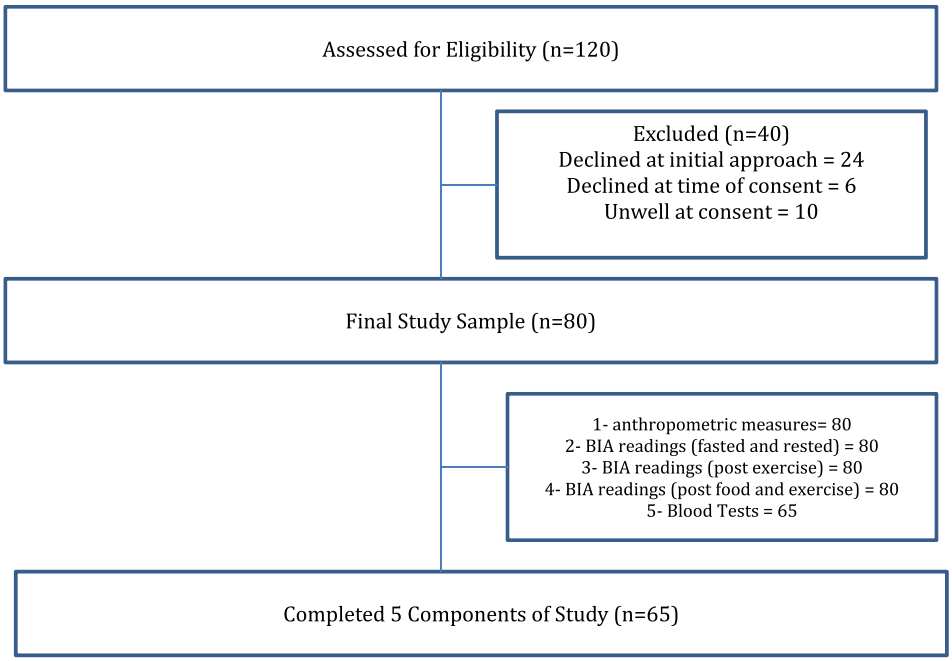

Fig. 1. Participant Flow: 80 patients were recruited of whom 66 fully completed the study.

Table 1
Key patient data.

	Number	Percentage
Age 18–34	11	13.75
Age 35–51	19	23.75
Age 52–68	28	35
Age 69–87	22	27.5
Male	46	57.5
Female	34	42.5
Pneumonia	7	8.75
Asthma	6	7.5
Bronchiectasis/lung abscess	4	5
COPD	4	5
Peptic ulcer complications	4	5
Ulcerative Colitis	4	5
Crohn's Disease	5	6.25
Complications of alcoholic liver disease	14	17.5
Short bowel syndrome	2	2.5
GI Malignancies	3	3.75
Other malignancies	2	2.5
Liver transplant	2	2.5
Acute Pancreatitis	2	2.5
Interstitial Lung Disease	3	3.75
Paracetamol Overdose	2	2.5
Investigations for jaundice	3	3.75
Investigations for diarrhoea	3	3.75
Other infections	4	5
Renal failure	2	2.5
Active Inflammation: Clinically/biochemically (CRP>10)	44	55
Ascites/fluid retention	7	8.75
Enteral/parenteral nutrition	3	3.75
Steroid medication	14	17.5
Well nourished (SGA)	33	41.25
Malnourished (SGA)	32	40
Severely malnourished (SGA)	15	18.75

4.3. SGA and PA compared to MUST and anthropometric measures

Both SGA and PA identified a higher proportion of patients at risk of malnutrition than MUST scores or individual anthropometric measurements. The study was not powered sufficiently to justify statistical analysis of these differences but there was an apparent association between triceps skinfold (TSF) and PA in that all but one of the patients regarded as having severe malnutrition from PA had a TSF below the 25th centile for normal populations. The exception was a patient with alcoholic cirrhosis and ascites whom the SGA also designated as having severe malnutrition, but whose TSF approached the 50th centile.

4.4. Biochemical markers of nutrition

In the study population the mean plasma citrulline was 33.2 μmol/L (SD 16.2), and for the nourished, malnourished and severely malnourished groups respectively was 30.2 (SD 8.6), 34.7 (SD 20.0), and 35.0 (SD 17.4) (Fig. 2). Compared with the nourished group, there were no statistically significant differences in plasma citrulline levels for the malnourished ($p = 0.331$) or severely malnourished ($p = 0.405$) groups. There was no association between plasma citrulline (per unit increase [μmol/L]) and SGA (Odds Ratio [OR] = 1.01, 95% CI 0.99–1.04, $p = 0.348$) (Fig. 2). Overall mean circulating transthyretin was 0.188 g/L (SD 0.84), and for the nourished, malnourished and severely malnourished groups respectively was 0.24 (SD 0.07), 0.16 (SD 0.06), and 0.17 (SD 0.10). Circulating transthyretin levels were significantly lower in the malnourished ($p < 0.001$) and severely malnourished groups ($p = 0.017$), compared with the nourished group. Circulating transthyretin levels (per unit increase [mg/L]) were significantly inversely associated with being malnourished or severely malnourished (compared with nourished) (OR = 0.98, 95% CI 0.97–0.99, $p = 0.001$) (Fig. 2). There was no significant association between transthyretin levels (per unit increase [mg/L]) and severe malnutrition (compared with the nourished and malnourished groups) (OR 1.00, 95% CI 0.99–1.01, $p = 0.777$). The predictive power of transthyretin was substantially inferior to that attributable to phase angle measurement. In 38% of cases severe malnutrition (SGA) would be missed by transthyretin used alone, and in 9% of cases a very low transthyretin (predictive of severe malnutrition)

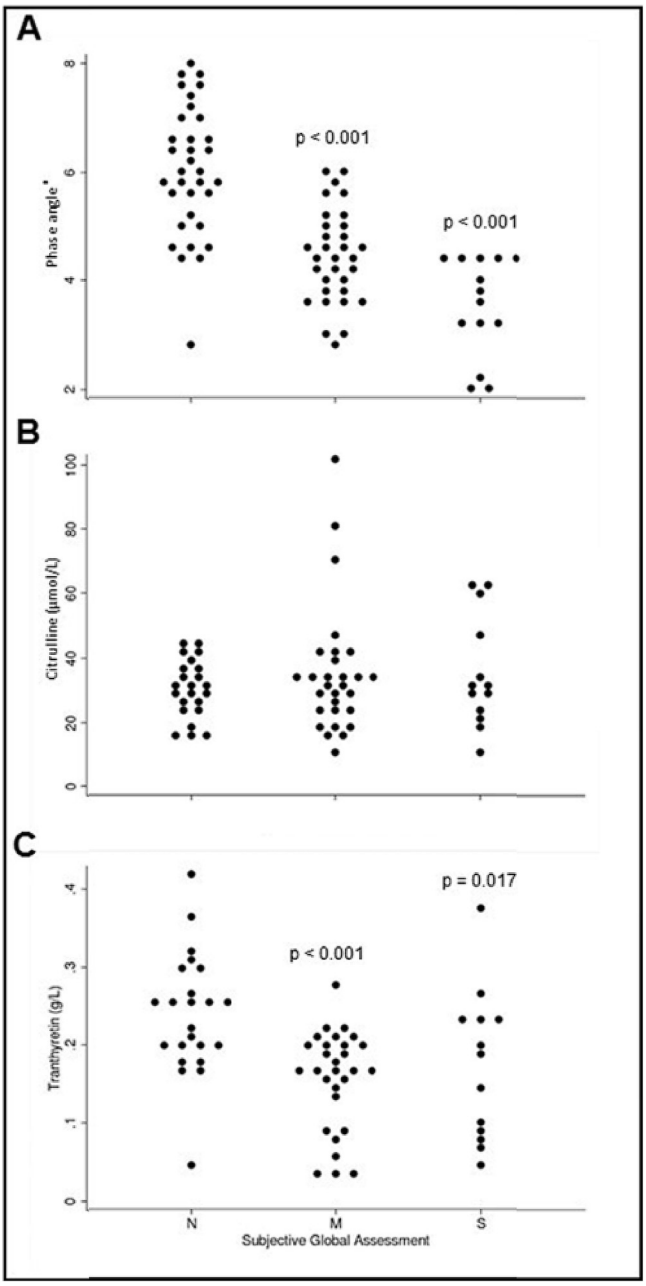

Fig. 2. Phase angle, plasma Citrulline (A) and Transthyretin (B) according to subjective global assessment of nutrition. Abbreviations: N, Nourished; M, Malnourished; S, Severely malnourished. p-values for comparison with nourished group. Mean Phase angle (SD) °for N, M, S groups respectively: 5.97 (1.20), 4.39 (0.86), 3.47 (0.88). Mean Citrulline (SD) (mmol/L) for N, M, S groups respectively: 30.2 (8.6), 34.7 (20.0), 35.0 (17.4). Mean Transthyretin (SD) (g/L) for N, M, S groups respectively: 0.24 (0.07), 0.16 (0.06), 0.17 (0.10).

occurred in patients who were considered to have normal nutritional status on SGA.

5. Discussion

Our results confirm that measurement of phase angle can detect malnutrition and that this can discriminate moderate from severe malnutrition when judged against subjective global assessment in a typical in-patient population [1]. Importantly, we demonstrate that current protocols requiring starvation and bed-rest are probably unnecessary. Circulating transthyretin was significantly associated with malnourished states, but the strength of the association was less than that for phase angle. Citrulline was not a good marker of nutritional status in this context.

The principal limitations of the study are its relatively small size and the inherent dependence on the subjectivity of the SGA. Systematic observer bias was minimised by recording SGA before BIA was performed. The researcher recording the SGA also performed the BIA in each case, and although it is unclear how the digital PA reading could be influenced in any way by the researcher there is always the potential for occult observer bias. It was not felt that sub-group analysis based on the data from individual researchers was warranted. As patients were studied on a single morning there was no loss to follow up, but reproducibility was not assessed.

Study subjects were not excluded because of ascites or marked fluid retention which are often considered contraindications to BIA. Informal analysis indicates that correlation of PA with SGA was then closely comparable to the correlation in our patients without fluid retention. This is of course not the first study to support the use of BIA in assessment of nutritional status [25], nor the first to find particular value from the standardized PA, in general [26], and in the context of disease states that substantially alter body fluid such as cirrhosis, and chronic renal failure [27–30].

At first sight it may seem surprising that PA and degree of malnutrition remain strongly associated in a context where most screening tools fail because they are confounded by the false impression that the total body weight (including retained fluid) reflects lean mass. PA however is a direct mathematical transformation of the electrophysiological data and is not reliant on any of the predictive equations otherwise applied by the BIA machine to determine (for example) lean body mass, which depend on assumptions of normal fluid distribution. The differentiation between malnutrition and severe malnutrition made on the basis of the PA value (<2 integers) is admittedly arbitrary and may need to be refined in future studies.

Our confident conclusion that unprepared measurement of PA is suitable for the clinical setting contrasts with the results of Slinde *et al* who found that eating a meal significantly affected the BIA readings on both multi-frequency and single frequency BIA machines for 2–4 h [15]. We know that the hospital breakfast spontaneously consumed by our patients had lower average nutritional content than the carefully controlled experimental meals used by Slinde *et al*, but see this as a strength of our assertion of clinical relevance in that typical patients taking their chosen breakfast showed no change in PA. Assuming a mean PA in the fasted and rested group of 4.9°, a difference in standard deviations between groups of 0.55°, with 80% power at the 5% level, the minimum difference in PA following food or exercise we could detect was 0.31°. While our numbers are relatively small and open to future challenge in other clinical settings, our study was nevertheless adequately powered to detect a small difference in PA.

Transthyretin has previously been identified as a marker of nutritional status [19] and our study supports these findings. While there was a statistically significant association between transthyretin and malnourished states, transthyretin could not distinguish severely malnourished subjects from those with improved nutritional status. Overall, PA performed better than transthyretin. It is possible that this advantage lay with PA because several of the patients studied had an alcohol dependency syndrome, given that alcohol can affect transthyretin levels. This advantage might be stronger still had patients been studied immediately after hospital admission when recent alcohol consumption will have been more likely. Steroid intake is also

Table 2
The association between baseline phase angle, circulating citrulline and transthyretin and nutritional status.

	SGA (n)			Proportional odds model		Partial proportional odds model			
						N vs M/S		N/M vs S	
	N	M	S	OR (95% CI)	p value	OR (95% CI)	p	OR (95% CI)	p
Phase angle									
Continuous scale	34	32	14	0.21 (0.12–0.37)	<0.001	–	–	–	–
By tertile					<0.001	–	–	–	–
2.0–4.3	2	15	13	1.00 (reference)	–	–	–	–	–
4.4–5.6	10	14	1	0.08 (0.02–0.31)	–	–	–	–	–
5.7–7.9	22	3	0	0.01 (0.001–0.04)	–	–	–	–	–
Plasma citrulline/mmol/L									
Continuous scale	23	29	13	1.01 (0.99–1.04)	0.348	–	–	–	–
By tertile					0.855				
10.2–26.6	8	10	4	1.00 (reference)	–	–	–	–	–
27.7–34.5	8	9	5	1.11 (0.37–3.33)	–	–	–	–	–
34.7–101.9	7	10	4	1.11 (0.36–3.42)	–	–	–	–	–
Plasma transthyretin/mg/L									
Continuous scale	23	29	13	–	–	0.98 (0.97–0.99)	0.001	1.00 (0.99–1.01)	0.777
By tertile							<0.001		0.757
30–94	2	14	6	–	–	1.00 (reference)	–	1.00 (reference)	–
169–201	8	12	2	–	–	0.18 (0.03–0.95)	–	0.27 (0.11–1.50)	–
231–273	13	3	5	–	–	0.06 (0.01–0.34)	–	0.31 (0.11–0.85)	–

Abbreviations SGA: subjective global assessment, CI. confidence interval, N: normally nourished, M: malnourished, S: severely malnourished.

known to affect the level of transthyretin in the blood; some of the patients included in the study were being treated with steroids and this too could have adversely affected the predictive value of the transthyretin results [17,18]. Analyses of circulating citrulline and transthyretin (n = 65) were more susceptible to type II error than for PA (n = 80) as there were fewer included subjects in the former.

Our data demonstrate that measurement of phase angle in unprepared hospital in-patients provides reliable information about their nutritional status, which is comparable to the time-consuming and operator-dependent subjective global assessment. It out-performs simple nutrition screening tests and the measurement of transthyretin (pre-albumin) and citrulline. Incorporation of phase angle into nutrition screening strategies should now be specifically explored.

Statement of authorship

All authors have participated and contributed to the research study. ELP and AF were involved in the design of the study. ELP, PM, TT, WYC were involved in data collection. JT and JD analysed blood samples. LA completed the statistical analysis. ELP, LA and AF interpreted the data. ELP draughted the manuscript. All authors contributed to the final manuscript.

STROBE Statement: checklist for observational studies completed.

Conflict of interest

The authors have no conflicts of interest to declare.

Funding sources

No external funding was granted.

Acknowledgements

The authors thank their colleagues on the staff of the gastroenterology and respiratory wards at the Norfolk and Norwich University Hospital and the patients who participated in the study.

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