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Research Article

The Potential of Phase Angle as a Nutritional Assessment Tool and Prognostic Factor in Patients with Gastrointestinal Cancers

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Abstract

Malnutrition is a common finding in patients with cancer and can significantly affect disease progress and patients' survival. Gastrointestinal Cancers (GIC) are amongst the most common cancer types. In gastroin-testinal cancer patients, the prevalence of malnutrition has been estimated to be around 39-67%. Body composition reflects the nutritional status. Bio-Impedance Analysis (BIA) is a noninvasive, time- and cost-effective technique to analyse body composition.

This review paper aims to critically summarise the currently available clinical data on the efficiency of the easily obtainable BIA measure, Phase Angle (PA), in the evaluation of malnutrition in GIC patients and on disease progression and prognosis.

PubMed database was thoroughly searched, in order to identify clinical studies that explore the role of BIA- derived raw data and weight loss on disease prognosis and progress, as well on assessing malnutrition.

Phase angle may be used as a nutritional screening tool in patients with gastrointestinal cancers. However, it cannot distinguish between stages of cachexia. Concerning the role of PA as a prognostic factor, current studies show that PA may be used as a prognostic factor of survival, yet further studies are needed for firm conclusions regarding post-operative complications and disease characteristics.

Due to the fact that gastrointestinal cancers are a group of various cancers, further studies should be undertaken, in order to evaluate the role of BIA and PA on all gastrointestinal cancer sites and types.

Keywords: Gastrointestinal cancer; Phase angle; Bioimpedance analysis; Malnutrition; Screening tool; Prognostic factor

Abbreviations

BIA: Bioimpedance Analysis; CRC: Colorectal Cancer; ECW/ICW: Extracellular/Intracellular Water; GIC: Gastrointestinal Cancer; NETs; Neuroendocrine Tumours; OS: Overall Survival; PA: Phase Angle; PG-SGA: Patient Generated-Subjective Global Assessment

Introduction

Malnutrition is a common finding in patients with cancer, even at diagnosis. Its incidence varies between 31- 87%, depending on cancer stage, histopathological type, treatment and patient [1,2]. Malnutrition can significantly affect disease progress and patient survival. Studies have shown that weight loss in cancer is associated with poor prognosis, poor quality of life, increased treatment-related side effects and reduced tumour response to treatment, as well as lower physical activity levels [3].

Weight loss may develop due to either elevated energy requirements, low energy intake or compromised nutrient absorption. In cancer patients, undernutrition may be attributed to various factors. Inflammation and catabolism due to tumour can lead to muscle wasting and body weight loss (4), while tumour gastrointestinal obstruction can compromise both food intake and absorption, as dysphagia, pain, and vomiting can be present. During treatment, eating related side-effects, such as low appetite, early satiety, nausea and/or vomiting, oral and intestinal mucositis with dysphagia, diarrhoea, haemorrhoids, anal fissures, and smell and taste changes may not only affect total energy intake, but also nutrient absorption, negatively affecting nutritional status, while poor patients' mental health state can affect their food and energy intake [5-7]. Weight loss at diagnosis has been associated with shorter failure-free and overall survival, while being identified as an independent prognostic factor [8].

Gastrointestinal cancers are amongst the common cancer types. Worldwide, colorectal cancer was the third most commonly diagnosed cancer in 2018, while stomach cancer was the 5th and oesophageal cancer was the 7th most common cancer diagnosed that year [9]. The same year, 10.2% of all cancer incidence (including non-melanoma skin cancer) in both sexes worldwide was due to colorectal cancer, 5.7% was due to stomach cancer and 4.7% was due to liver cancer and 3,2% was due to oesophageal cancer.

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Malnutrition and cachexia are quite common in gastrointestinal cancers and early detection and management is important [10]. In fact, malnutrition risk is up to 80% [10], while it varies between gastrointestinal cancer site and stage [11], as well as screening tool [12]. In gastrointestinal cancer patients, the prevalence of malnutrition was estimated to be around 39.3% for colon/rectum cancer patients, 60.2% for oesophagus and/or stomach cancer patients and 66.7% for pancreas cancer patients [11], while in gastrointestinal cancer patients under chemotherapy it is estimated at 52% [13].

An important issue concerning malnutrition is under-diagnosis [13], despite the fact that nutritional status screening is advised to be performed at diagnosis [14], and body composition analysis can lower the risk of treatment toxicity [15], while BMI alone cannot distinguish fat mass from fat-free mass, and cannot take into account weight loss [16].

Body composition reflects the nutritional status. Bio-Impedance Analysis (BIA) is a noninvasive, time- and cost-effective technique to analyse body composition [17]. BIA can be used to assess the body composition of patients of all ages, independently of their physical and mental health status, as this measurement is fast and easily obtainable, with patients just having to step on the scale-analyser and hold the electrodes. BIA results and raw data are obtained immediately. Notably, BIA is currently used in various clinical settings, from hospitals to dietetic clinics; hence, it is easy to find a clinician or dietitian that has access to body composition analysers. Additionally, most body composition analysers are portable.

Due to the fact that the results of BIA are based on regression equations for healthy individuals, it has been proposed that raw data derived by BIA can be useful to this population [18]. Raw BIA parameters are reactance and resistance, from which phase angle (PA / Phase angle = arc - tangent reactance/resistance x 180°/ π) can be retrieved [19]. Both PA reflects both nutritional and hydration status, being also considered as measure of cell membrane function and integrity [18-20]. A high PA score reflects good function of cellular membrane, while a low PA is associated with cellular apoptosis and a decrease in content of cellular matrix [21]. PA is considered to be a useful prognostic tool in various diseases [22], critically ill patients [23], and especially in cancer patients [17,24], while it has been related with body weight changes in cancer patients undergoing radiotherapy [25]. BIA analysis has been used as a means to evaluate the nutritional status, as well as the course of treatment [26,27]. It has also been identified as a prognostic factor in head and neck [28,29] colorectal [30] and lung [31] cancer patients, as well as in advanced-stage cancer patients [32,33]. Moreover, current body composition analysers display PA in their results. However the importance of adopting different cutoffs has been highlighted oftentimes [22,34].

In view of the above considerations, this review paper aims to critically summarise and discuss the currently available clinical data on the efficiency of the easily obtainable phase angle in the evaluation of malnutrition in gastrointestinal cancer patients, highlighting its role on disease progression and prognosis.

PubMed database was thoroughly searched using relative keywords (cancer, phase angle, BIA, bio-impedance, gastrointestinal, colorectal, gastric, liver, oesophagus, stomach, liver, gallbladder, pancreas), in order to identify clinical studies that explore the role of phase angle on disease prognosis and progress, on assessing malnutrition. Inclusion criteria were studies in humans with GIC, and papers written in English language.

Results

Phase angle as a nutritional screening and assessment tool in gastrointestinal cancer

Phase Angle has been used as a nutritional screening and assessment tool in cancer patients [17,24,35] and has been previously shown to be able to distinguish between nourished and malnourished patients with oesophageal [34], stomach [34] and colorectal cancer [36]. Recent studies highlight the value of PA on diagnosing malnutrition, while proposing cut-off points for diagnosing malnutrition [34].

Souza et al. [37] conducted a cross-sectional study with 197 Colorectal Cancer (CRC) patients, 29 of whom were later diagnosed with sarcopenia. Multivariable analysis revealed that PA was amongst the independent predictors of sarcopenia in this patient group. Another recent retrospective study explored the use of BIA as a means to evaluate malnutrition in patients with colorectal disease, most of whom had cancer (82.5%). The postoperative evaluation of 40 patients showed that PA was associated with malnutrition. Malnourished patients had lower PA, with an optimal PA cutoff point at 6.0°, where the tool showed 76.5% sensitivity, 87.0% specificity, 81.3% positive predictive value and 83.4% negative predictive value [38]. Data of 73 stage III and IV CRC patients were used in a retrospective study [36], aiming to evaluate the relationship between SGA and BIA measures. Well-nourished patients had a statistically significantly higher median phase angle, compared to those who were malnourished (6.12° *vs.* 5.18°). A phase angle cut-off point at 5.2° was 51.7% sensitive and 79.5% specific whereas a cut-off of 6.0° was 82.8% sensitive and 54.5% specific in detecting malnutrition. A phase angle cut-off of 5.9° had high diagnostic accuracy in men who did not respond to primary treatment for advanced colorectal cancer.

In another recent study in 153 geriatric GIC patients, PA was lower in those who were malnourished than those who were not malnourished [39]. A study by Ozorio et al. [16] explored the relation of cachexia defined by Fear on and different nutritional assessment tools, namely PG-SGA, PA, and handgrip strength. 101 GIC patients on chemotherapy with mean age 61.8 ± 12.8 years enrolled, of whom 32.6% were malnourished according to their BMI, while 63.3% were severely or moderately malnourished according to PG-SGA, 60.4% had decreased handgrip strength, and 57.4% had low PA. All tools, including PA, were associated with cachexia, however, PA could not identify between different stages of cachexia. At a cutoff of 5.3° the tool showed 72% sensitivity and 77.5% specificity.

In a recent study, 38 patients with stomach, colorectal, and biliary cancer with cachexia (weight loss of ≥ 5% over a 6 month period), under chemotherapy underwent BIA. PA was significantly lower in patients, compared to healthy controls, and significantly lower in females than males. Male cancer patients, who had lower PA, also had lower intracellular water levels compared with healthy controls. A lower Extracellular/ Intracellular Water (ECW/ICW) ratio was highly correlated with increased PA in cancer patients. The authors

Table 1: Studies concerning the value of Phase Angle as a nutritional screening tool.

Participants	Results	Reference
43 adult patients with Oesophageal cancer (n=30) Stomach cancer (n=13)	PA was different between nourished patients and those with suspected/ moderate malnutrition (SGA-A *vs.* SGA- B) and nourished patients and those with severe malnutrition (SGA-A vs SGA-C)	Da Silva et al. [34]
101 patients with oesophageal cancer treated with chemo-radio-therapy	A malnutrition prediction model was constructed and the only predictor for deterioration in nutritional status was fat free mass index. PA could not predict malnutrition in this patient group	Rietveld et al. [43]
153 geriatric GIC patients	PA was lower in those who were malnourished than those who were not malnourished	Hopanci et al. [39]
101 GIC patients on chemotherapy	PA was associated with cachexia, however, PA could not identify between different stages of cachexia. At a cutoff of 5.3° the tool showed 72% sensitivity and 77.5% specificity.	Ozorio et al. [16]
38 patients with stomach, colorectal, and biliary cancer with cachexia, under chemotherapy	PA was significantly lower in patients, compared to healthy controls, and significantly lower in females than males. PA may be suitable marker for gender- specific changes in cell composition and health status	Yoon et al. [40]
197 Colorectal Cancer (CRC) patients	PA was an independent predictors of sarcopenia	Souza et al. [37]
40 patients with colorectal disease - 82.5% had cancer	PA was associated with malnutrition	Nishiyama et al. [38]
73 stage III and IV colorectal cancer patients	Well-nourished patients had a statistically significantly higher median phase angle, compared to those who were malnourished (6.12° *vs.* 5.18°)	Gupta et al., [36]
54 adult patients - 27 With Hepatocellular Carcinoma (HCC)	PA was negatively correlated with nutritional risk and ECW/ICW and positively with handgrip strength.	Pagano et al. [41]
43 cirrhotic patients with HCC	PA was one of the most sensitive tools in the diagnosis of malnutrition.	Silva et al. [42]

Table 2: The prognostic role of PA on survival and clinical outcomes in patients with gastrointestinal cancers.

43 adult patients with oesophageal (n=30) and stomach cancer (n=13)	PA was not a prognostic factor of mortality in patients with oesophageal and stomach cancer.	da Silva [34]
628 palliative care patients of whom 39.5% had gastric cancer	PA was an independent prognostic factor of survival, while patients with sarcopenia had lower PA than those without sarcopenia (3.9° *vs.* 4.1°)	Perez Camargo et al. [46]
452 palliative care patients of whom 39.2% had gastric cancer	PA was significantly positively correlated with survival.	Perez Camargo et al. [47]
210 elderly patients who had undergone gastrectomy due to gastric cancer	PA was an independent prognostic factor for overall and severe complications.	Yu et al. [52]
52 patients with stage IV colorectal cancer	PA is a prognostic factor in patients with advanced colorectal cancer.	Gupta et al. [44]
250 elderly colorectal cancer patients	PA >5° was associated with better prognosis and a relative hazard of death 0.456	Barao et al. [45]
50 patients with advanced colorectal cancer (23 patients) and patients on follow-up after CRC treatment (27 patients)	PA was not different between the two patient groups. PA was not a prognostic factor for survival.	Cavagnari et al. [49]
84 adult patients with colorectal cancer scheduled to undergo surgery	PA was not found to be a prognostic factor for complications.	Mauricio et al. [51]
54 adult patients - 27 with hepatocellular carcinoma (HCC)	There was a trend toward lower survival in patients with HCC, according to the PA cutoff point of 5.1°. PA an independent prognostic indicator for cirrhosis and may be related to survival in these patients.	Pagano et al. [41]
51 HCC patients	Screening questionnaires and BIA measurement are superior to anthropometric measurements to identify malnutrition. PA is an independent prognostic factor in patients with HCC at a cut-off point of 4.8°.	Schutte et al. [48]
58 stage IV pancreatic cancer patients	PA is a prognostic factor in advanced pancreatic cancer	Gupta et al. [30]
83 patients with Neuroendocrine Tumours (NETs) originating from the gastro-entero-pancreatic tract and 83 healthy matched controls	A lower PA was significantly correlated with more aggressive tumour, metastases, and progressive disease.	Barrea et al. [50]

concluded that ECW/ICW ratios and PA may be suitable markers for gender-specific changes in cell composition and health status [40].

Moreover, PA has been shown to be a sensitive nutritional assessment tool in Hepatocellular Carcinoma (HCC) patients [41,42] and was negatively correlated with nutritional risk and ECW/ICW and positively with handgrip strength [41].

Da Silva et al. [34] undertook a study to investigate the relationship between different nutrition screening/ assessment tools, complication and survival in patients with oesophageal and stomach cancer. They showed that PA was different between nourished patients, those with Suspected/Moderate Malnutrition (SGA-A *vs.* SGA-B), nourished patients, and those with severe malnutrition (SGA-A *vs.* SGA-C), according to the SGA tool.

On the other hand, a prospective cohort study with 101 patients with oesophageal cancer treated with Chemo-Radio-Therapy (CRT) failed to show that PA can diagnose risk for malnutrition. A prediction model was constructed to identify predictive parameters for deterioration in nutritional status (weight loss of >5% and/or decline in fat free mass of ≥1.4 kg) during CRT. The only predictor for deterioration in nutritional status during CRT was higher fat free mass index. Those with a higher fat free mass index were at increased risk of deterioration in nutritional status [43].

The vast majority of studies has shown that phase angle can be used as a nutritional screening tool in patients with gastrointestinal cancers. However, it may not be able to distinguish between stages of cachexia. Additionally, due to the fact that gastrointestinal cancers are a group of various cancers that affect the body and the nutritional

status differently, further studies should be undertaken, in order to evaluate the role of BIA and PA on all GI cancer sites and types.

Phase angle as a prognostic factor of clinical outcomes in gastrointestinal cancer

Phase angle has been studied and considered to be a prognostic factor for survival and other clinical outcomes in cancer.

Gupta et al. [30,44] evaluated the prognostic role of PA in advanced pancreatic and colorectal cancer in two earlier studies. In the first study, fifty-eight stage IV pancreatic cancer patients underwent BIA. Patients with phase angle <5.0° had a median survival time of 6.3 months, while those with phase angle >5.0° had a significantly longer median survival time of 10.2 months [44]. Similarly, case series of 52 patients with stage IV colorectal cancer were evaluated. Patients with a phase angle ≤5.57° had a median survival of 8.6 months while those with a phase angle >5.57° had a significantly longer median survival of 40.4 months, indicating that PA is a prognostic indicator in this patient group [30]. In another retrospective study, in 250 elderly colorectal cancer patients PA >5° was associated with better prognosis and a relative hazard of death 0.456 [45].

In palliative cancer patients, the role of PA on Overall Survival (OS) was explored in 628 patients, 39.5% of whom had gastric cancer. Patients with sarcopenia has a shorter OS than those without sarcopenia (71 *vs.* 98 days) and PA was an independent prognostic factor of survival, while patients with sarcopenia had lower PA than those without sarcopenia (3.9° *vs.* 4.1°) [46]. Another study, by the same scientists, on 452 palliative care patients of whom 39.2% had gastric cancer, an average PA of 4.0° and mean BMI at 22.84 kg/m^2. The average survival of patients with PA ≤ 4° was 86 days, while in the group with PA > 4°, was significantly longer at 163 days. PA showed significant positive correlation with both survival and BMI [47].

As far as patients with HCC are concerned, PA was found to be an independent factor of survival at a cut-off point of 4.8° [48], while in another study with HCC patients a trend for shorter survival at a cut-off point of 5.1° was observed [41].

However the study by Cavagnari et al. [49] showed different results. They investigated the role of BMI, body composition, PA, PG-SGA, adiponectin levels, and vitamin D levels on characterization and differentiation of patients with advanced CRC and patients with a history of CRC. Participants had either advanced colorectal cancer (23 patients) or were on follow-up after CRC treatment (27 patients). The mean PG-SGA score was significantly higher in advanced colorectal cancer patients, compared to those on follow up, and was a prognostic factor of survival in patients with advanced colorectal cancer. However, PA was not different between groups, and not a prognostic factor for survival. In addition to this, the study by da Silva et al. [34] also showed that PA was not a prognostic factor of mortality in patients with oesophageal and stomach cancer.

Hence, although the majority of studies support that PA may be a prognostic tool for longer patient survival, further studies are needed on patients who are not on palliative care or at the fourth stage of the disease, while taking into account treatment stage.

Concerning disease progress, Barrea et al. [50] evaluated the nutritional status of patients with Neuroendocrine Tumours (NETs) originating from the gastro-entero-pancreatic tract in a cross-sectional case- control observational study with 83 patients and 83 healthy matched controls. A lower PA was significantly correlated with more aggressive tumour, metastases, and progressive disease [50], while in liver cancer patients PA was an independent prognostic factor for chirrosis [41].

Considering post-operative complications, the prognostic value of PA and other tools were explored in the study by Mauricio et al. 84 adult patients with cancer of the colon or rectum, scheduled to undergo surgery were enrolled. PA was not found to be a prognostic factor for complications. Low muscle mass and strength were the strongest variables associated with complications [51]. In another study however, PA was an independent prognostic factor for overall and severe complications. More to the point, 210 elderly patients who had undergone gastrectomy due to gastric cancer were enrolled in a study to evaluate the prognostic role of PA on postoperative complications. Multivariate analysis showed that two or more comorbidities and hypoalbuminemia were independent risk factors for overall complications, and female sex was independent risk factor for severe complications. A low PA and total gastrectomy were independent risk factors for both overall and severe complications. Hence, BIA is suggested to be performed in order to assess the risk of postoperative complications in elderly patients with gastric cancer [52].

As a result, there are currently few and conflicting evidence on the role of PA on post-operative complications, yet the populations under study were different concerning cancer site and age.

Conclusions

Phase Angle is a relatively novel nutritional assessment and screening tool, which has been used in various clinical settings over the last few years, including cancer patients. Cancer patients are at high risk of malnutrition and cancer cachexia. Studies have investigated the role of PA on assessing malnutrition, as well as on being a prognostic factor of survival and post-operative complications.

More to the point, the vast majority of currently available studies show that PA can be used as a malnutrition screening and assessment tool in patients with gastrointestinal cancers, and specifically oesophageal, stomach, liver, biliary and colorectal cancer, while it can also predict sarcopenia in colorectal cancer patients. However, PA was unable to distinguish the stages of cachexia [16], as well as stages of malnutrition regarding SGA [34].

In patients with oesophageal and stomach cancer the study by da Silva et al. showed that PA could distinguish between nourished patients and malnourished patients, according to SGA [34], but another study on oesophageal cancer patients showed that PA was unable to distinguish patients at risk for malnutrition [43]. Hence, concerning oesophageal cancer further studies are needed to form a safe conclusion regarding the value of PA on the nutritional status of this patient group.

Regarding the need to adopt new cut-off points for evaluating malnutrition, patients with gastrointestinal cancers, few studies have been undertaken, and support different PA cut-off points. Different cut-offs for each cancer type may be optimal, yet further, more cancer

type-specific studies must be undertaken.

Furthermore, studies have also been undertaken regarding the prognostic role of PA on survival and complications in GIC patients. A lower PA was found to have a prognostic value concerning survival in advanced pancreatic and colorectal cancer patients, as well as in palliative care patients with gastric cancer and HCC patients. However, two studies showed that PA was not a prognostic factor for survival in patients with advanced or with history of CRC and in patients with oesophageal and stomach cancer, may due to the different cancer types and stages included in the analyses. Yet, a low PA was independent risk factors for both overall and severe complications in elderly patients who had undergone gastrectomy, but not in adult patients with colorectal cancer. Conflicting evidence on the role of PA on post-operative complications may be due to the heterogeneity of the populations under study.

Studies across clinical settings do use Bioimpedance Analysis to evaluate PA as a measure of nutritional status [20,30,53]. As most studies in the present review include patients with various gastrointestinal cancers, which do have a different effect on nutritional intake and malnutrition risk, it is important to note that further studies are needed to clarify the malnutrition assessment value, the prognostic value and new cutoffs of PA, with evaluations per cancer type and stage.

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