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Phase angle as predictor of chemotherapy toxicity severity in breast cancer patients

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ABSTRACT

Introduction: Breast cancer is the leading cause of cancer-related mortality in Brazilian women. Chemotherapy, while effective, often induces debilitating side effects and toxicity. Phase angle (PA), derived from bioelectrical impedance, is a non-invasive biomarker associated with cellular health and prognosis. This study aimed to evaluate PA variation in breast cancer patients undergoing chemotherapy, correlating it with side effect severity, tumor molecular subtype, and patient age. **Methods:** An observational, longitudinal, retrospective study included 30 breast cancer patients treated with chemotherapy in Cascavel, PR, Brazil (2022-2023). PA was measured pre- and post-chemotherapy using a Sanny BIA1011-AF device. Side effects were graded (0-2 vs. 3-4) via CTCAE. Statistical analysis used t-tests, χ^2 test, and repeated measures ANOVA ($p<0.05$). **Results:** A significant PA reduction was noted from pre- to post-chemotherapy across the cohort ($p<0.001$). No main effect of age or molecular subtype on PA was observed. However, a significant interaction ($p=0.017$) between side effect grade and assessment time revealed that patients with grade 3-4 effects experienced a substantially greater PA decline (mean difference 0.8545 units; $p<0.001$). **Conclusions:** Chemotherapy for breast cancer leads to phase angle reduction. The magnitude of this reduction significantly correlated with side effect severity, independent of molecular subtype or age. PA is a sensitive indicator of chemotherapy's physiological impact and toxicity.

KEYWORDS: breast cancer; chemotherapy; electric impedance; drug toxicity.

INTRODUCTION

Breast cancer is the most common female cancer worldwide and the leading cause of cancer death in women[1]. The various breast cancer treatments, although increasingly innovative and effective, can be aggressive and cause side effects for patients, which can reduce their quality of life[2]. Patients undergoing chemotherapy experience various side effects and possible toxicities, such as neutropenia, anemia, thrombocytopenia, leukopenia, nausea and vomiting, diarrhea, constipation, mucositis, weight gain, alopecia, fatigue, and musculoskeletal effects, among others[3]. The oxidative stress caused by breast cancer and its treatments, such as radiation, chemotherapy, hormone therapy, and surgery, causes inflammation which can lead to toxicity, altered body composition and loss of muscle mass and strength, potentially promoting sarcopenia, a factor in a worse prognosis in breast cancer[4,5].

Phase angle (PA), data obtained from bioelectrical impedance, is a simple, rapid, non-invasive, and low-cost test. It uses a formula based on resistance and reactance to measure energy dynamics in cells. This indicator is related to cellular function and health, making PA an important predictor of tissue functionality. It is used in prognosis and morbidity assessment. Low PA can be strongly associated with impaired nutritional and functional status in several types of cancer, including breast cancer[6,7]. It is possible that the effects of the disease and its treatment decrease PA, damaging cell membranes and causing cancer-related cachexia and inflammation[2].

Breast cancer treatment, while increasingly effective, often entails a series of side effects and toxicities that compromise patients' quality of life and may lead to discontinuation or modification of the treatment regimen. Given this scenario, the search for accessible and non-invasive biomarkers that allow monitoring the physiological impact of chemotherapy and tracking the risk of toxicity becomes a necessity. In this context, PA has proven to be a promising tool for monitoring chemotherapy toxicity, offering the potential to optimize clinical management, personalize supportive interventions, and consequently improve the safety and tolerability of cancer treatment.

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The objective of this study was to evaluate the variation in PA obtained by bioelectrical impedance analysis in breast cancer patients undergoing chemotherapy and to correlate these variations with the occurrence and severity of treatment side effects, tumor molecular subtype, and patient age, aiming to establish PA as a sensitive marker of the physiological impact and toxicity of chemotherapy.

METHODS

We conducted an observational, longitudinal, retrospective study using data collected from medical records provided by a cancer center in Cascavel, Paraná State in Brazil, which contained information on cancer type, patient treatment, nutritional status, outcomes, and disease follow-up.

Initially, 94 medical records of patients diagnosed with breast cancer who received care at the clinic between 2022 and 2023 were evaluated. For inclusion in the study, only women over 18 years of age, diagnosed with breast cancer, who underwent chemotherapy, and who had complete nutritional monitoring, including bioelectrical impedance recordings at the beginning and end of treatment, were selected. Patients who were not of appropriate age (under 18 years of age), without a diagnosis of breast cancer, those diagnosed but not undergoing chemotherapy, those who did not receive nutritional monitoring, those without sufficient data for the proposed analysis, or those who were lost to follow-up during the study period were excluded. After applying these inclusion and exclusion criteria, the final study sample consisted of 30 patients (Figure 1).

The main objective of the study was to investigate PA as a possible predictor of toxicity in breast cancer patients undergoing chemotherapy. To this end, data collected from medical records were analyzed to determine whether there was a relationship between PA and the extent of side effects and toxicity. The medical records contained data related to the type of cancer, the treatment received by the patients, bioimpedance data, age, side effects, and the patient's progress during and after treatment. These data were tabulated in a Microsoft Excel spreadsheet and statistically analyzed. PA before and after chemotherapy was compared, seeking a relationship with the side effects and toxicity described in each patient's medical records. Side effects were classified according to the Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE v5.0, published in 2017) scale developed by the National Cancer Institute (NCI). In addition to PA and side effects, the relationship between age and PA and tumor molecular subtype and PA was analyzed.

The PA measurement was performed using a tetrapolar bioimpedance device (BIA1011-AF - SANNY BIOIMPEDANCE - WITH PHASE ANGLE - SERIAL: G192041007). All patients were advised to prepare for the test, which included: not using diuretics in the previous seven days (under medical supervision), fasting for at least four hours before the test, not consuming alcoholic beverages in the previous 48 hours, not engaging in physical activity in the 24 hours before the test, not using saunas in the eight hours before the test, and not consuming coffee or diuretic teas 24 hours before the test. Furthermore, women during their menstrual period were advised not to undergo the test. The test was performed at various times according to the patient's availability, wearing comfortable, light clothing, and in the supine position. Data were collected before and after chemotherapy treatment.

For data description, quantitative variables were presented as mean (± standard deviation) and median [minimum, maximum], while qualitative variables were expressed as absolute values and percentages. The statistical significance of comparisons between groups was assessed using Student's t-test for normally distributed data and the Mann-Whitney U test for nonparametric data. For categorical variables, the χ^2 test was used, with continuity correction when applicable. Repeated measures analyses were performed using repeated measures analysis of variance (ANOVA), with Tukey's post hoc tests to explore significant differences, and the paired t-test for comparisons between two paired conditions. In all tests, a p-value<0.05 was considered statistically significant. All statistical analyses, as well as the construction of graphs and tables, were conducted using JAMOVI software, version 2.5.0, based on the R language.

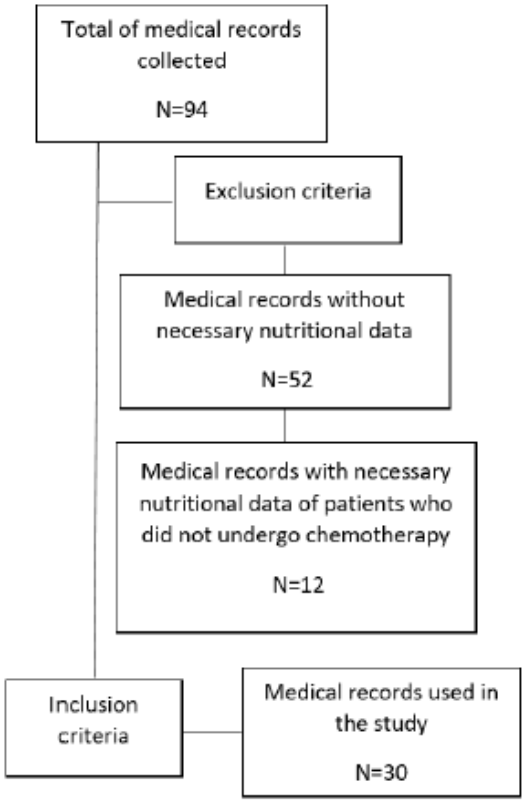


Figure 1. Flowchart of final sample.

This study was approved by the Research Ethics Committee of the Assis Gurgacz University Center, with CAAE protocol identification number: 80654124.6.0000.5219, approved on the Brazil/CEP Platform. As required for CEP approval, a waiver of the informed consent form was signed given the retrospective design of the study.

RESULTS

The study sample consisted of 30 participants, allocated into two groups according to the degree of side effects presented: Grade 0-2 (n=19) and Grade 3-4 (n=11). An initial analysis of demographic characteristics revealed no statistically significant differences between the groups, indicating homogeneity (Table 1).

The mean age was similar between the Grade 0-2 group (Mean=50.3; SD=10.0) and the Grade 3-4 side effect group (Mean=49.7; SD=12.5), as indicated by the t-test (p=0.895). These results suggest that the groups were comparable with respect to their baseline characteristics.

Table 1. Epidemiological and clinical characteristics of patients included in the study, according to the degree of toxicity.

Epidemiological profile of sample	0-2 (n=19)	3-4 (n=11)
Age		
Mean (SD)	50.3 (10.0)	49.7 (12.5)
Median [Min, Max]	53.0 [34.0, 68.0]	44.0 [34.0, 68.0]
Angle-1		
Mean (SD)	5.21 (0.593)	5.23 (0.785)
Median [Min, Max]	5.17 [4.26, 6.41]	5.28 [3.95, 6.38]
Angle-2		
Mean (SD)	4.90 (0.636)	4.38 (0.672)
Median [Min, Max]	4.92 [3.62, 5.95]	4.53 [3.35, 5.37]
Molecular subtype (A or B)		
A – Luminal A	3 (15.8%)	0 (0%)
B – Luminal B	9 (47.4%)	4 (36.4%)
C – Pure HER2-positive	4 (21.1%)	1 (9.1%)
D – Triple-negative	1 (5.3%)	5 (45.5%)
E – Luminal B with HER2 overexpression	2 (10.5%)	1 (9.1%)
Had chemotherapy?		
Adjuvant	8 (42.1%)	2 (18.2%)
Neoadjuvant	11 (57.9%)	9 (81.8%)
Age group, years		
31-40	4 (21.1%)	2 (18.2%)
41-50	4 (21.1%)	5 (45.5%)
51-60	9 (47.4%)	1 (9.1%)
60+	2 (10.5%)	3 (27.3%)

Grade 0-2: mild to moderate; Grade 3-4: severe.

Phase angle vs. degree of side effects

The comparison between PA and side effect grade revealed a statistically significant interaction between the severity of the side effect and the time of PA assessment (pre- vs. post-chemotherapy), with p=0.017, as determined by ANOVA. For this analysis, patients were divided into two groups: the first, comprising those who presented mild to moderate symptoms (CTCAE grades 0 to 2), with little interference with daily activities; the second, patients who developed more severe symptoms (CTCAE grades 3 to 4), indicating significant limitations in daily life and the need for medical intervention. It is important to emphasize that no patient in the study reached grade 5 severity, which culminates in death. PA was compared at the pre- and post-chemotherapy times for each of these groups (Figure 2).

Patients with grade 3-4 side effects were observed to have a significantly greater decline in PA. Post hoc analysis revealed that, for this group, the mean difference between pre-chemotherapy PA and post-chemotherapy PA was 0.8545 (0.506–1.203) units, with a Tukey p-value less than 0.001, denoting a highly significant reduction in PA over the course of treatment. In contrast, for patients with grade 0-2 side effects, the variation in PA did not show the same magnitude of statistically significant decline. Five patients included in the study (approximately 16%) had temporary discontinuation of chemotherapy due to side effects; all belonged to the group that developed grade 3 or 4 adverse events. Consequently, the results indicated that patients who experienced more severe side effects experienced a more marked decline in PA.

Phase angle vs. age

The evaluation of the relationship between PA and patient age during chemotherapy for breast cancer revealed specific patterns. First, a significant difference was observed between the pre-chemotherapy phase angle (pre-CT) and the post-chemotherapy phase angle (post-CT) for the sample studied (Figure 3).

To investigate the influence of treatment time and age group on PA, a repeated-measures ANOVA was conducted. The results

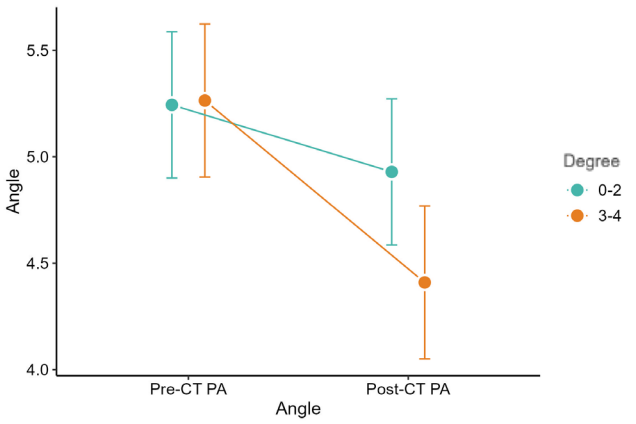


Figure 2. Comparison of pre-chemotherapy phase angle and post-chemotherapy phase angle with the degree of side effects.

demonstrated a statistically significant main effect of time (p<0.001), indicating an overall reduction in PA from the first measurement (pre-CT PA) to the second (post-CT PA) across the entire patient cohort.

No main effect of age group was identified (p=0.168), suggesting that overall none of the age groups presented consistently higher or lower PA than the others. This finding indicates that age, per se, was not a determining factor for baseline or mean PA levels between the groups.

A statistically significant interaction effect between time and age group was detected (p=0.027). This result indicates that the magnitude of the PA change (pre-CT PA to post-CT PA) differed according to the age group. Although all age groups showed a downward trend in PA, the 41-50 age group showed a slightly more pronounced reduction. However, it is important to emphasize that, given the sample size, this particular difference did not reach statistical significance in isolation.

In summary, chemotherapy was shown to be a predominant factor in the reduction in PA. Age, while not determining the overall level of PA, exerted a subtle modulation on the response to treatment toxicity, evidenced by the interaction effect, indicating that the intensity of the PA decline may vary slightly between age groups.

Phase angle vs. molecular subtype

The initial analysis of PA variation in relation to cancer molecular subtypes did not demonstrate statistical significance (p=0.153) when comparing pre- and post-chemotherapy time points comprehensively. Therefore, it was decided to regroup patients into two main categories for more detailed analysis: one group comprising Luminal A/B tumors and the other comprising Luminal B tumors with HER2 overexpression and negative hormones (including triple-negative and HER2-pure). This division was strategically defined on the basis of intrinsic biological aggressiveness profiles and the intensity of chemotherapy regimens associated with each subtype. It was considered that the Luminal A/B group, generally less aggressive, contrasts with the Luminal B group with HER2 overexpression and negative hormones, which comprises more aggressive subtypes and frequently subjected to more intensive systemic treatments, which could influence the physiological response assessed by PA in a different way (Figure 4).

With this new categorization, the evaluation revealed that the time factor (pre-chemotherapy PA vs. post-chemotherapy PA) was statistically significant (p=0.001), indicating an overall reduction in PA across the sample after chemotherapy. However, the interaction between the time factor and tumor molecular type (according to the new classification) was not statistically significant. Although the group with HER2-overexpressing Luminal B and negative hormone levels showed a visually more pronounced decline in PA, this difference did not reach reliable statistical significance. This lack of significance in the interaction may be related to the small sample size.

A post hoc test confirmed the significant difference between the pre- and post-chemotherapy time points, with a mean difference in PA of 0.523 (0.298–0.748). These findings corroborate the graphic illustration, which demonstrates a general pattern of PA decline. In summary, despite the visual variations, the statistical analysis indicates that there was no significant difference in the magnitude of the change in PA between the two major molecular groups studied.

DISCUSSION

In this study, we sought to investigate and characterize the relationships between PA and age, molecular type, and the presence of side effects or associated clinical conditions in breast cancer patients undergoing chemotherapy. The choice of PA as the focus of analysis is justified by its growing recognition as a noninvasive, rapid, and low-cost biomarker, promising for assessing cellular integrity, nutritional status, and clinical prognosis in various health conditions, as widely highlighted in the scientific literature[1,2,6,7]. In an oncological setting, where treatment can induce severe toxicities, the search for accessible markers that allow monitoring the

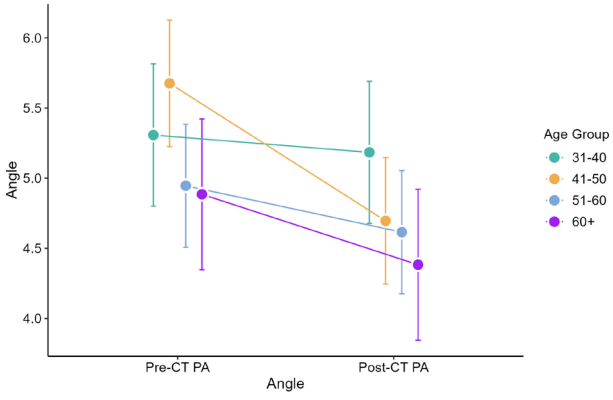


Figure 3. Comparison of pre-chemotherapy phase angle and post-chemotherapy phase angle with patient age.

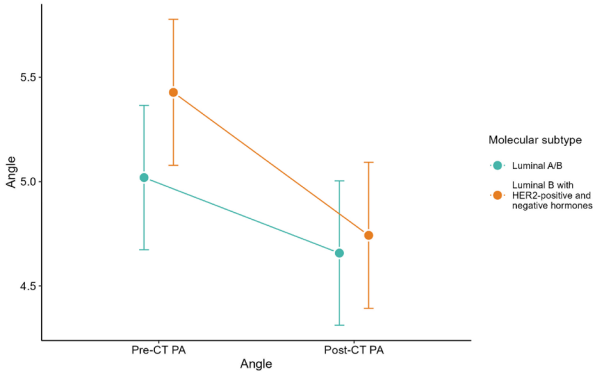


Figure 4. Comparison of pre-chemotherapy phase angle and post-chemotherapy phase angle with breast cancer molecular subtype.

physiological impact of chemotherapy and tracking the risk of toxicity is crucial. Understanding the factors that modulate PA is, therefore, essential for its effective application in risk assessment and monitoring the individual health of cancer patients[3].

The results obtained in this study demonstrated that although PA undergoes a physiological decline with advancing age in general populations[2,8], in the present sample of breast cancer patients undergoing chemotherapy, age was not a determining factor for baseline PA levels or the extent of their reduction. This finding suggests that, in the context of an aggressive systemic treatment such as chemotherapy, the direct impact of treatment on cellular integrity and functionality, reflected by PA, may outweigh age-related variations.

Regarding the impact of tumor molecular type on PA, the initial comparison between breast cancer subtypes did not demonstrate statistical significance (p=0.153). Therefore, it was decided to group the patients into two broad profiles: Luminal A/B tumors and a more aggressive group comprising Luminal B HER2-positive, HER2-pure, and triple-negative tumors. This categorization was based on their distinct biological aggressiveness and the often more intensive chemotherapy regimens associated with each type, according to established guidelines[5]. Although the time factor was significantly associated with the reduction in PA (p=0.001), the interaction with the grouped molecular type was not statistically significant. This result diverges from studies such as that of Justa et al.[9], which suggest a smaller reduction in PA in luminal tumors, associated with more favorable histopathological characteristics. The non-significance observed in our study, despite a visual trend toward a greater decline in the more aggressive group, may be attributed to the small sample size, which may have limited the statistical power to detect subtle differences. It is plausible that the intensity of different chemotherapy regimens—such as AC-T for HER2-negative luminal tumors, AC-TC for triple-negative tumors with the addition of carboplatin, and TC-HP for HER2-pure tumors with trastuzumab and pertuzumab[5]—exerts such a pronounced cellular impact that the resulting damage (and, consequently, the reduction in PA, which reflects cell membrane integrity and tissue health) becomes comparable between subtypes, regardless of their intrinsic aggressiveness.

The results of this study reveal that PA is established as a non-invasive and sensitive biomarker for monitoring chemotherapy toxicity in breast cancer, demonstrating a highly significant association between its decline and the severity of side effects. The magnitude of this decline varied substantially between patient groups, with a statistically significant interaction between the severity of the side effect and the time of PA assessment (p=0.017). In particular, individuals with grade 3-4 side effects (the most severe, according to CTCAE) exhibited a significantly greater decline in PA, with a mean difference of 0.8545 units between pre- and post-chemotherapy PA (Tukey's p<0.001). This significant decrease in PA suggests a substantial impairment of cellular integrity and functionality in response to chemotherapy toxicity[4]. Frequently reported adverse symptoms, such as neutropenia, anemia, nausea, vomiting, and fatigue, are commonly associated with metabolic dysfunction, systemic inflammation, and muscle wasting, which are reflected in decreased PA[9,10]. Clinically, the observation that the most debilitated patients throughout treatment corresponded to those with the smallest initial PAs and the greatest declines in PA reinforces the usefulness of PA as a sensitive biomarker of treatment aggressiveness and the body's ability to tolerate it. This conclusion is consistent with the vast literature that uses PA as an independent predictor of morbidity and mortality and as an indicator of global cellular health in disease contexts[4,6].

Nevertheless, this study has limitations inherent to its retrospective, cross-sectional design that prevent direct causal inferences. Furthermore, the small sample size (n=30) limited the statistical power of the analyses, particularly regarding age and molecular subtype. The analysis of medical records may contribute to potential information bias regarding toxicity classification. Future studies suggest prospective, longitudinal studies with larger cohorts that monitor PA during each chemotherapy cycle. This approach would enable early interventions to prevent and treat side effects. Integrating PA with other biomarkers can also deepen our understanding of cellular and bodily health, paving the way for new clinical applications and guidance for personalized interventions[11].

CONCLUSIONS

In conclusion, this study demonstrated that chemotherapy for breast cancer resulted in a reduction in PA in patients. Notably, the intensity of this decrease correlated significantly with the severity of side effects experienced. In contrast, PA variation was not significantly associated with the tumor's molecular subtype or the patient's age. These findings establish PA as a sensitive marker of the physiological impact of chemotherapy, especially regarding toxicity and adverse effects.

AUTHORS' CONTRIBUTIONS

ISC: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. ASO: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation. APGS: Data curation, Formal analysis, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing. MLB: Data curation, Formal analysis, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing. DSG: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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