Author's response to reviews

Title: Bioelectrical impedance phase angle as a prognostic indicator in breast cancer

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Author's response to reviews:

Reviewer: Aluisio J D Barros

Reviewer's report:

Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

1. The research question posed by the authors is relevant and well defined. The idea of using BIA as a prognostic factor for survival in cancer patients is interesting and may lead to changes in clinical practice. However, the strong link made by the authors between BIA phase angle and nutrition is not entirely suitable since phase angle measures cell membrane integrity related to various physiological aspects that are not only nutritional. AS ADVISED, THE ARGUMENTS ON THE LINK BETWEEN BIA PHASE ANGLE AND NUTRITIONAL STATUS HAVE BEEN SOFTENED SIGNIFICANTLY. FOR EXAMPLE, NOWHERE IN THE REVISED MANUSCRIPT DO WE DESCRIBE BIA PHASE ANGLE AS A SOLE MARKER OF NUTRITIONAL STATUS.

2. The introduction presents a long report on diet and other nutritional aspects as prognostic factors in breast cancer. On the other hand, several studies that showed BIA phase angle to be a prognostic factor for different conditions were not mentioned, and comments in this area were generally brief. Since what phase angle measures is not specifically or exclusively nutrition, my suggestion is that the introduction gives less emphasis to diet and more to phase angle as a prognostic tool in other diseases. THE PARAGRAPH 3 OF THE
3. A description of follow-up times should be included in results. It is not clear from the methods whether all patients had equal follow-up periods or not, and if not what was its distribution. THE DETAILS ON FOLLOW TIMES HAVE BEEN INCLUDED IN THE RESULTS.

4. Phase angle is defined as \( \text{Phase Angle} = (\text{Resistance}/\text{Capacitance}) \times (180/#) \), but, its standard definition is \( \text{PA} = \arctan(\text{reactance}/\text{resistance}) \times (180/\pi) \). It is necessary to correct or explain why a different equation is used. RJL. Also, in the literature \( X_c \) has been used as an abbreviation for reactance (or capacitive reactance) and not for capacitance. AS SUGGESTED, CAPACITANCE HAS BEEN REPLACED WITH REACTANCE. THE FORMULA WE USED WAS AS PER THE REFERENCES CITED IN THE PAPER.

5. Several nutritional indicators were measured at baseline, as stated in methods, and none used in the analyses. It would be interesting to assess how SGA or other indicators would change the effect of phase angle. THANKS FOR THIS OBSERVATION. BUT THE FOCUS OF THIS STUDY WAS TO LOOK ONLY AT PHASE ANGLE IN RELATION TO SURVIVAL. THE EFFECT OF OTHER NUTRITIONAL INDICATORS WILL BE DISCUSSED IN SEPARATE PAPERS.

6. Departure of linearity was not tested for phase angle as a continuous variable in the Cox model. It is necessary to check model fit in this aspect.

7. An alternative approach to dicotomising phase angle using the sample median would be to use the reference values published in Barbosa-Silva MC, Barros AJ, Wang J, Heymsfield SB, Pierson RN, Jr. Bioelectrical impedance analysis: population reference values for phase angle by age and sex. Am J Clin Nutr 2005 Jul; 82: 49-52. Patients could then be classified into groups such as <-2, -2--<-1, >=-1 standard deviations, giving further insight into phase angle's effect. The value used corresponds roughly to the 5th percentile for women aged 40-49 years. This approach would resolve one limitation mentioned in the discussion (line 268). THANKS FOR THIS INTERESTING SUGGESTION. WE HAE ACTUALLY EXPLORED THE SUITABLE CUT-OFFS OF PHASE ANGLE USING ROC ANALYSES IN OUR OF OUR OTHER PAPERS THAT IS CURRENTLY UNDER SUBMISSION TO A DIFFERENT JOURNAL.

8. The paragraph starting at line 214 is a bit confusing. The text suggests some incongruence of results, but they all indicate a positive association of phase angle with survival. By the way, the use of population reference values would
avoid the use of different cut-off points for phase angle improving comparability between studies. WHILE DIFFERENT STUDIES HAVE USED DIFFERENT CUT-OFFS OF PHASE ANGLE, THEY HAVE ALL CONCLUDED THAT HIGHER PHASE ANGLE VALUES ARE ASSOCIATED WITH BETTER SURVIVAL. THAT’S THE POINT WE WANTED TO HIGHLIGHT IN THE DISCUSSION.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. A better caption is needed for Table 1, since it presents the outcome as well. It should also present the age distribution of the sample. THE TITLE HAS BEEN CHANGED TO PATIENT CHARACTERISTICS. AGE DISTRIBUTION HAS ALSO BEEN INCLUDED.

2. The second column label in Table 2 should read “Median survival in months”. SUGGESTED REVISION MADE.

3. Reporting of p-values should use at least 3 decimal places and be consistent for all results. AS SUGGESTED, ALL P-VALES NOW USE AT LEAST 3 DECIMAL PLACES.

Reviewer: Ursula Kyle

Reviewer’s report:
The paper is well written and poses the question well. The methods are appropriate and well described. The discussion and conclusions are well balanced and adequately supported. THANK YOU.

Minor essential revisions

Discussion
Although the authors mentioned that phase angle depends on age, sex, and body mass characteristics, the authors should make it clear that the cut-off of phase angle in this study might be different in other study populations (older subjects, men etc). AS SUGGESTED, WE HAVE ADDED THAT CAUTION IN THE DISCUSSION SECTION.

Please shorten the discussion on page 4, third paragraph, lines 84 to 103. The discussion of dietary intake does not directly related to your study, thus can be abbreviated. AS SUGGESTED, THIS PARAGRAPH HAS BEEN SUBSTANTIALLY SHORTENED.

Reviewer: Robert J MacInnis

Reviewer’s report:
A well-written report, and the research is of good standard, but there are a few
revisions that I recommend.

Major Compulsory Revisions
1. The follow-up time is a little unclear - was there a cutoff date for all participants followed? Were there any persons lost to follow-up? If so, do they differ in characteristics? THANKS FOR THIS OBSERVATION. THE CUT-OFF DATA OF FOLLOW-UP FOR ALL PARTICIPANTS WAS MAY 07 BECAUSE THAT’S WHEN THE ANALYSIS WAS DONE. THIS CLARIFICATION HAS BEEN INCLUDED IN THE REVISED PAPER.

2. Were there men in the analysis? If so, how many? Were sex-specific analyses performed? Such analyses would need to be reported. NO THERE WERE NO MEN IN THE ANALYSES. IT HAS NOW BEEN CLEARLY STATED UNDER THE METHODS SECTION THAT THIS STUDY WAS PERFORMED IN FEMALE BREAST CANCER PATIENTS ONLY.

3. Were tests performed to check whether proportional hazard assumptions were violated for any of the measures? If so, then models would have to be altered accordingly. THE ASSUMPTIONS WERE MET FOR ALL MEASURES.

4. It was mentioned in the discussion that it was preferable to perform analyses from date of diagnosis, but the sample size would be reduced. It would be nice to see these results in any case, even though the confidence intervals would be wide. THE EXACT DATE OF DIAGNOSIS FOR 178 PATIENTS WAS NOT AVAILABLE. WE BELIEVE 81 IS AN INADEQUATE SAMPLE SIZE FOR SUCH ANALYSES. WE WILL SEPARATELY REPORT THE RESULTS ON OUR NEWLY DIAGNOSED PATIENTS IN A FEW MONTHS WITH AN UPDATED PATIENT COUNT.

5. For those who had progressive disease, was their time since initial diagnosis available? If so, this could be incorporated into the model. AS MENTIONED ABOVE, THE EXACT DATE OF DIAGNOSIS WAS NOT AVAILABLE FOR PATIENTS WITH PROGRESSIVE DISEASE.

Minor Essential Revisions
1. The p-values for stage and prior treatment history in paragraph 3 of the results appear incorrect. THE TYPOS HAVE BEEN CORRECTED AND THEY NOW MATCH WITH THE RESULTS IN THE TABLE.

2. In Table 3, Stage at diagnosis has the referent category as Stage II and III. I presume it should be I and II? What was done with missing stage? THANKS FOR THIS OBSERVATION. WE HAVE CORRECTED THE TYPO IN TABLE 3. PATIENTS WITH MISSING STAGING INFORMATION WERE EXCLUDED FROM THE ANALYSES.
3. Other co-variables in the model should be described in Table 3. TABLE 3 HAD ONLY THREE VARIABLES IN THE MODEL: PHASE ANGLE, STAGE AT DIAGNOSIS AND TREATMENT HISTORY. ONLY THOSE VARIABLES WERE CONSIDERED IN THE MULTIVARIATE ANALYSIS THAT WERE FOUND TO BE SIGNIFICANT UPON UNIVARIATE ANALYSIS.