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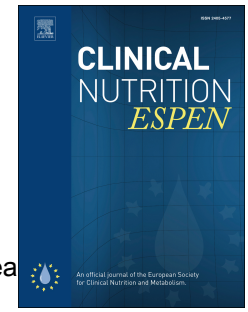

Bioelectrical impedance vector analysis (BIVA) as a method to compare body composition differences according to cancer stage and type

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Title

Bioelectrical impedance vector analysis (BIVA) as a method to compare body composition differences according to cancer stage and type

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Abstract

Background & Aims

Bioelectrical impedance vector analysis (BIVA) is a non-invasive method of measuring human body composition . This offers the potential to evaluate nutritional and hydration states in cancer. Analysis of BIVA data using z-score (the number of standard deviations away from the mean value of the reference group) has the potential to facilitate comparisons between different cancer types.

The aim of this study was to use the BIVA Reactance (R) / Reactance (Xc) z-score method to evaluate body composition differences in cancer, using data from previously published BIVA studies.

Methods

Previous studies using BIVA in cancer were identified from the literature. Bioimpedance measures were analysed using the BIVA RXc z-score graph. The mean vector impedance measures from the studied populations were transformed into standard deviates (with respect to the mean and standard deviation of the reference populations). Body composition was classified according to vector placement (i.e. normal athletic, cachectic, oedematous and dehydrated).

Results

Seven male and three cancer female populations were evaluated. Body composition was classified as normal for the majority (n=5), followed by cachexia (n=4) and athletic (n=1) respectively. Variation in body composition for the studied populations appeared to be related to factors, such as gender, disease type and severity.

Conclusions

The BIVA RXc z-score method has potential to evaluate body composition differences between cancer groups. This method can study body composition, according to cancer type, stage, gender and ethnicity. Limitations of the method relate to issues appropriate reference populations and variability between bioimpedance analysers. Better body composition assessment has the potential to personalise therapeutic, nutrition and hydration management. Further work is essential to facilitate in-depth evaluation in these areas, in order to achieve meaningful use of the BIVA method in clinical practice.

Key words

Bioelectrical impedance vector analysis; Bioelectrical impedance analysis; nutritional assessment; cancer; body composition; palliative care

Introduction

People with advanced cancer commonly experience body composition changes (i.e. fat, bone, water and muscle). [1-4]. Evidence demonstrates that cancer patients with reduced physical function report poorer quality-of-life[5] and shorter life expectancy compared to other patients.[6]Bioelectrical impedance analysis (BIA) is a non-invasive method of measuring human body composition (i.e. analysis of fat, bone, water and muscle).[7] BIA, delivers a low frequency electrical current and works on the principle that fluid and cellular structures will provide different levels of resistance to an electrical current as it passes through a living system.[7] BIA provides the following measurements: Resistance (R - Ohms), assessing cellular hydration; Reactance (Xc - Ohms), assessing tissue integrity and Phase Angle (PA - degrees), representing the arc-tangent between R and Xc (PA is a useful indicator of health and prognosis.[7]). BIA technology has been used to evaluate hydration and nutrition in several populations.[7, 8]

Bioelectrical impedance vector analysis (BIVA) to assess body composition in advanced illness

Statistical vector analysis of BIA data enables further analysis of human body composition to be conducted.[9] Bioelectrical impedance vector analysis (BIVA) uses graphical vectors to analyse BIA data.[8] Using this method, impedance (Z) is plotted as a vector from its components R (X axis) and Xc (Y axis), after being standardized by height (H). The RXc graph represents the sex and race-specific tolerance intervals of a comparative reference population. Tolerance ellipses are plotted on the RXc graph to represent the 50%, 75% and 95% centiles (i.e. confidence intervals) for the population. (Figure 1 - *The RXc graph with*

95%, 75% and 50% tolerance ellipses. Reproduced and modified with permission).[10] The advantage of this method is that it allows information to be obtained simultaneously about changes in tissue hydration or soft-tissue mass, independent of regression equations, or body weight. Therefore, BIVA can be interpreted accurately even if patients are at extremes of weight or volume distribution. BIVA has been used to study hydration status in a variety of different diseases[11-19] and to undertake general body composition assessments in lung cancer[18, 20] and cancers of the head and neck.[21] Our previous research used the BIVA method to examine associations between hydration status, symptoms and survival in advanced cancer patients.[22]

BIVA RXc z-score analysis facilitates comparisons between populations

Statistical conversion of BIVA measurements to z-scores enables researchers to compare body composition of different study populations.[23] Piccoli et al[23] used this method to compare BIVA data for a variety of disease groups. To date, no studies have used the BIVA RXc z-score method to synthesise cancer populations evaluated with BIVA. Consequently, there is potential to use the BIVA Z score method to evaluate body composition by cancer type and severity. Such information will potentially help support nutritional assessment and management in cancer.

Aim

To determine the feasibility of the using the BIVA RXc z-score method to compare body composition in cancer populations using published bioimpedance data.

Materials and Methods

A systematic review reporting BIVA in advanced cancer (published by Nwosu et al 2013[8]) was used to identify previous studies using BIVA to evaluate body composition in advanced cancer. Further, an electronic search of the literature using MEDLINE, EMBASE and Pubmed (combining keywords of “bioelectrical impedance vector analysis" and “Neoplasms[MesH]”, limited to English language and humans) was conducted to identify relevant studies.

Inclusion criteria for studies

Articles were eligible for review provided that they involved the use of BIA in adult humans with cancer. The following data was required for the z-score analysis: (i) R/H (Ohm/m) and Xc/H (Ohm/m) mean for the studied population, (ii) studied population size, (iii) sex-specific bioimpedance data and (iv) details of the reference population used for the analysis. Minimum standards for the reference population were as follows: the total sample size n≥100, the R/H (Ohm/m) mean, R/H (Ohm/m) standard deviation (SD), Xc/H (Ohm/m) mean and Xc/H (Ohm/m) SD. The Picolli 1995 reference population (Caucasian Europeans, males (n=354) and females (n=372) aged 18 - 85 years, body mass index (BMI) 16 -31 kg/m^2, Italy, analyser = Akern-RJL systems [24]) was used for studies which did not meet the minimum reference standard. We selected the Piccoli data as it was the most commonly selected reference population for studies evaluating the BIVA method.

Exclusion criteria for studies

The following articles were excluded: Non English studies; those reporting paediatric populations; absent data to facilitate the BIVA Z score analysis (see inclusion criteria).

BIVA software and z-score analysis

BIVA was conducted using software developed by Professor Antonio Piccoli, University of Padova.[25] The mean vector impedance measures for study populations were transformed into standard deviates with respect to the mean and standard deviation and compared against their reference population.[24] The z-score is the number of standard deviations away from the mean value of the reference group.[26] Z-scores can provide information about an individual measured score, relative to others in the distribution.[27]

Transformation of the BIVA measurements to z-scores facilitates comparison between different conditions and diseases (Figure 2). Using the RXc z-score graph, individuals within the 50% tolerance ellipse are considered to have normal body composition, whereas those in the 75% and 95% tolerance ellipses are abnormal.[25]

Vectors were plotted on the RXc z-score graph to facilitate data comparison. Vectors plotted within the 50% tolerance ellipse were considered normal. Based on data from the Piccoli study,[23] the BIVA RXc z-score graph was divided into four quadrants to classify body composition of populations within the 75% and 95% (i.e. abnormal) tolerance ellipses. These quadrants were (i) *Athletic* (high cell mass), top left, (ii) *Cachexia* (low cell mass), bottom right; (iii) *Oedema*, bottom left and (iv) *Dehydrated*, top right (Figure 2). Body composition was determined according to the plotted vector position. Further details on the equations used to calculate the RXc Z score graph analysis are available in the appendix.

Ethical Statement

This study was a secondary analysis of previously published research. Therefore, ethical approval was not required.

Results

The literature search returned 15 full text articles using BIVA in people with cancer (Figure 3). Two of these articles were rejected as they are not specific to patients with advanced cancer. Two studies (Lundberg et al[28] and Gnagnarella et al[29]) were excluded as insufficient data was available to enable the RXc z-score analysis to be conducted. Of the remaining eleven studies, some presented the same BIVA data. These included two different studies, which both reported data for the same breast cancer sample.[30, 31] Similarly, two studies reported data for the same head and neck cancer sample.[21, 32] We grouped the relevant studies together to avoid confusion. Consequently, nine of the eleven eligible studies were included. These nine studies provided data for seven male and three female populations (Table 1). The studies described different cancer types and stages, which included advanced cancer of different origin;[22] lung cancer (including a sample of patients in remission),[18, 20] breast cancer,[30] head and neck cancer[21, 33] and gynaecological cancer.[34] Details of patient demographics, type of analyser and BIVA z-score analysis are presented in Table 1.

BIVA RXc z-score analysis

The reference population of Piccoli et al[24] was used as the chosen reference population for the authors of the Cardoso[34] and Nwosu studies. However, the seven populations described by Toso et al[18, 20] and Malecka-Massalska[21, 31, 35] [30, 32] used control groups with sample sizes of n<100 as a reference. We used the Piccoli data[24] as a reference population for these studies. Consequently, the Piccoli reference population was used as the reference for all studies in this paper.

The z-score analysis is presented in Figure 4 and Table 2 (supplementary file). Five populations were normal (50% tolerance ellipse). These were the male and female cohorts with various cancers (Nwosu et al 2016[22]), males with lung cancer in remission(Toso el al 2003[18]), males patients with stage III lung cancer (Toso el al 2000 [20]) and females with gynaecological cancer (Cardoso et al 2017[34]). Comparatively greater cell mass was noted in females with the newly diagnosed breast cancer[30] (the vector was superior to the 95% tolerance ellipse of the athletic quadrant) had. Four groups were cachectic (vectors within the 75% and 95% tolerance ellipse). This included males with stage IV lung cancer (Toso et al 2000[20] - 75% tolerance ellipse), males with local and disseminated lung cancer(Toso et al 2003[18] - 75% tolerance ellipse), and two populations of males with head and neck cancer (Malecka-Massalska et al 2013[33]– 75% tolerance ellipse, and Malecka-Massalska et al 2012, 2014[21, 32] - 95% tolerance ellipse). .

Discussion

Main findings

Seven male and three cancer female populations were evaluated. Body composition was classified as normal for the majority (n=5), followed by cachexia (n=4) and athletic (n=1) respectively. Variation in body composition for the studied populations appeared to be related to factors, such as gender, disease type and severity.

Strengths and uniqueness of this study

This is first study to use the BIVA z-score method to compare body composition in cancer populations, using data from previously published bioimpedance data. BIVA offers advantages over traditional methods of body composition assessment, due to its non-invasive nature and simplicity. BIVA has methodological advantage over traditional BIA

calculations due to its independence of regression equations (which lack accuracy in cancer[7]). Furthermore, BIVA can facilitate longitudinal assessments to evaluate body compositionchanges over time. These properties are useful to evaluate nutrition and hydration in people affected by cancer, who are unable to tolerate more invasive methods of assessment. This research demonstrates the potential to use published BIVA data for larger analysis.

Comparison with previous work

The only previous study to use BIVA RXc z-scores in cancer was the Piccoli et al 2002.[23] Piccoli plotted data from the vector point for males with stage IV lung cancer (Toso et al 2000[20]) within the cachexia quadrant (75% tolerance ellipse). Our data builds on Piccoli's study and describes how, in addition to Toso's stage IV lung cancer data, three other populations were also classified as cachectic. This included a lung cancer sample with local and disseminated disease,[18] and two head and neck cancer cohorts[21, 32, 33]). The vectors for the advanced cancer population described by Nwosu et al[22] (although plotted within the normal 50% ellipse) were in a similar position to the lung cancer studies by Toso et al, [18, 20]. This suggests similarity between these groups (i.e. low muscle mass, with risk of cachexia), even though body composition was classified as normal. Therefore, interpretation of BIVA Rxc z-score data requires consideration of clinical factors in addition to BIVA.

Previous work illustrates how patients with cancer are prone to develop cachexia as their condition progresses.[1, 36] However, data about the stage of cancer was only available for two populations. It is possible that stratification of data by cancer stage may have demonstrated that individuals with more severe cancer were more likely to be cachexic.

Furthermore, assessments at different points in the disease trajectory may demonstrate changing body composition over time.

Our data demonstrates that body composition appeared to be related to cancer type, disease severity and gender.[37] For example, females with breast[30] and gynaecological cancers[34] had increased cell mass compared to other populations (demonstrated by more superior vector placement). Two factors may explain this difference. Firstly, individuals with breast and gynaecological cancer were comparatively younger than other groups (the mean age for the breast and gynaecological cancer groups were 53 and 60 years respectively, whereas most other populations were aged >60 years). Secondly, these patients were recruited at diagnosis, whereas participants in other studies were recruited later in their illness.

Limitations

A limitation of this study is that nutritional screening tools were not used in all studies, which makes nutritional based comparisons difficult. The Subjective Global Assessment (SGA - a simple bedside method of assessing the risk of malnutrition [38]) was used in the majority studies. Only one study (Cardoso et al[34]) reported body mass index (BMI) data according to the requirements of the European Society for Clinical Nutrition and Metabolism (ESPEN) malnutrition criteria.[39] Therefore, our ability to evaluate how BIVA RXc z-scores relates to nutritional states is limited.

A small number of studies were evaluated in this analysis and the majority of participants included in the studies were from white, European or North American populations, which limits our ability to extrapolate the findings. The under-representation of non-white groups in these studies may be due to various factors, such as language and cultural barriers.[40]

Further, as this analysis only included English language studies, it is possible that studies using BIVA in different cultural contexts were excluded.

The lack of BIVA research in females limits the ability to extrapolate results to women. Females differ physiologically to males (generally more body fat, less body water, shorter height and reduced muscle mass compared to men[41, 42]). Of the three studies including women, two studied female specific cancers (breast[30, 31], cervical[34]) and one studied with a mix of cancer types.[22] Therefore, no studies in the literature provide meaningful female-specific BIVA data for any cancers, other than those affecting the breast and cervix.

Our findings are limited by a lack of information about the reasons why reference populations were chosen Reference populations may not be representative of the studied population. This is problematic with the Cardoso et al[34] study, which used an inappropriate reference population (European white adults) for their analysis of a Brazilian Pardo (mixed race) sample.[34] It is likely this population was chosen due to the lack of other suitable reference populations. Furthermore, seven populations used small control groups (n<100) as their reference, which are inappropriate due to their small size. Although we used the Piccoli population as the reference for these studies, other reference population may have been more appropriate. This demonstrates the challenges of using the BIVA Z score method appropriately when there is variability about how reference populations are selected.

Different bioimpedance analysers were used throughout the studies included in this analyser. This may result in slight differences in reactance and resistance values which may alter the BIVA z-score interpretation. Finally, an inherent limitation of the BIVA method is that it is a qualitative assessment method which does not provide absolute values of body composition metrics.[8] Therefore, the method is unable to provide quantitative data on

body composition variables (e.g. fat free mass, and fluid volume). This is why stratification of BIVA data according to clinical variables is important (e.g. disease stage, type and ethnicity), in order to determine clinically meaningful outcomes.

Implications to clinical practice and policy

This analysis supports previous data that describes how body composition in cancer is related to a number of factors (e.g. stage, type of disease).[36, 43, 44] This study demonstrates the potential to use the BIVA RXc z-score method to undertake comparative, multi-group, body composition analysis, which could be useful to compare differences in cancer according to disease stage and type. This has the potential to personalise therapeutic, nutrition and hydration based interventions according to an individual's physiology. Although the BIVA RXc z-score method has potential use in clinical practice, we are unable to recommend its routine use in clinical practice (in cancer), due to the limited number of studies using the method and a lack of data to inform clinical interpretation.

Future research possibilities

Further research studies using bioimpendence are needed to evaluate differences in cancer, according to disease type, stage, ethnicity and gender. In order to improve the clinical usefulness of BIVA, future bioimpedance studies should report all the relevant data (and standard deviations) required to conduct BIVA[45] (i.e. age (years), Height (m), BMI (Height $(H)^2$/m), weight(kg), R (Ohm), R/H (Ohm/m), Xc (Ohm), Xc/H (Ohm/m), PA (degrees)). Researchers should justify the reasons for the choice of reference populations, stating why the chosen population is best suited for their analysis. Inclusion of this information will enable researchers to conduct BIVA analyses without needing to contact investigators for further information. Researchers should aim to develop larger, appropriately powered,

reference populations, to facilitate stratification (by age, gender, ethnicity and other clinical factors). As a priority, futures studies should generate data for non-white and female individuals.

Conclusions

The BIVA RXc z-score method can be used to evaluate body composition in people with cancer. This method can be used to conduct analysis of body composition according to different variables such as cancer type, stage, gender and ethnicity. Improved assessment will lead to better understanding of the physiological and biological processes of advanced cancer. Consequently, BIVA may help healthcare professionals to personalise therapy in patients with cancer according to their physiology.

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Conflict of Interest Statement

The authors declare that there is no conflict of interest.

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Author Contribution Statement

The author's responsibilities were as follows.

Research design: ACN

Data collection: ACN

Statistical analysis: ACN, TFC

Paper writing: ACN, CM, SM

Supervision: CM, SM, AV, JE

Critique and review of the final manuscript: ACN, CM, SM, TFC, SS, AV, JE

List of abbreviations used

BIA (bioelectrical impedance analysis), BIVA (bioelectrical impedance vector analysis), CAH, (clinical assisted hydration), ECOG (Eastern Cooperative Oncology Group performance status), H (height - m), M (mean), R (resistance - Ohm), R/H (resistance normalized by the height - m), Xc (reactance - Ohm); Xc/H (reactance normalized by height), RXc, (resistance/reactance); TBW (total body water), FFM (fat free mass), FM (fat mass), PA (phase angle - degrees), ESPEN (European Society for Clinical Nutrition and Metabolism), BMI (Body Mass Index - height/weight^2 [kg/m^2]).

References

1. Skipworth RJE, Stewart GD, Dejong CHC, Preston T, Fearon KCH. Pathophysiology of cancer cachexia: Much more than host–tumour interaction? Clinical Nutrition. 2007;26(6):667-76. doi: https://doi.org/10.1016/j.clnu.2007.03.011.
2. Sarhill N, Mahmoud FA, Christie R, Tahir A. Assessment of nutritional status and fluid deficits in advanced cancer. AmJHospPalliatCare. 2003;20(6):465-73.
3. Sarhill N, Walsh D, Nelson K, Davis M. Evaluation and treatment of cancer-related fluid deficits: volume depletion and dehydration. SupportCare Cancer. 2001;9(6):408-19.
4. Duren DL, Sherwood RJ, Czerwinski SA, Lee M, Choh AC, Siervogel RM, et al. Body composition methods: comparisons and interpretation. Journal of diabetes science and technology. 2008;2(6):1139-46. Epub 2009/11/04. PubMed PMID: 19885303; PubMed Central PMCID: PMC2769821.
5. Buffart LM, Kalter J, Sweegers MG, Courneya KS, Newton RU, Aaronson NK, et al. Effects and moderators of exercise on quality of life and physical function in patients with cancer: An individual patient data meta-analysis of 34 RCTs. Cancer Treatment Reviews. 2017;52:91-104. doi: https://doi.org/10.1016/j.ctrv.2016.11.010.
6. Brown JC, Harhay MO, Harhay MN. Physical function as a prognostic biomarker among cancer survivors. British journal of cancer. 2015;112(1):194-8. Epub 2014/11/14. doi: 10.1038/bjc.2014.568. PubMed PMID: 25393366; PubMed Central PMCID: PMCPMC4453612.
7. Barbosa-Silva MC, Barros AJ. Bioelectrical impedance analysis in clinical practice: a new perspective on its use beyond body composition equations. CurrOpinClinNutrMetab Care. 2005;8(3):311-7.
8. Nwosu AC, Mayland CR, Mason SR, Khodabukus AF, Varro A, Ellershaw JE. Hydration in advanced cancer: can bioelectrical impedance analysis improve the evidence base? A systematic review of the literature. J Pain Symptom Manage. 2013;46(3):433-46.e6. Epub 2012/12/04. doi: 10.1016/j.jpainsymman.2012.08.018. PubMed PMID: 23200189.
9. Piccoli A, Rossi B, Pillon L, Bucciante G. A new method for monitoring body fluid variation by bioimpedance analysis: the RXc graph. Kidney Int. 1994;46(2):534-9.
10. Piccoli A, Nigrelli S, Caberlotto A, Bottazzo S, Rossi B, Pillon L, et al. Bivariate normal values of the bioelectrical impedance vector in adult and elderly populations. The American journal of clinical nutrition. 1995;61(2):269-70. Epub 1995/02/01. PubMed PMID: 7840061.
11. Piccoli A. Bioelectric impedance measurement for fluid status assessment. ContribNephrol. 2010;164:143-52.

12. McDonald JJ, Chanduvi B, Velarde G, Cama R, Diaz F, Carrillo L, et al. Bioimpedance monitoring of rehydration in cholera. Lancet. 1993;341(8852):1049-51.
13. Bozzetto S, Piccoli A Fau - Montini G, Montini G. Bioelectrical impedance vector analysis to evaluate relative hydration status. 2010;25(1432-198X (Electronic)):329-34.
14. Codognotto M, Piazza M, Frigatti P, Piccoli A. Influence of localized edema on whole-body and segmental bioelectrical impedance. Nutrition. 2008;24(6):569-74.
15. Nescolarde L, Piccoli A, Roman A, Nunez A, Morales R, Tamayo J, et al. Bioelectrical impedance vector analysis in haemodialysis patients: relation between oedema and mortality. Physiol Meas. 2004;25(5):1271-80.
16. Piccoli A. Bioelectric impedance vector distribution in peritoneal dialysis patients with different hydration status. Kidney Int. 2004;65(3):1050-63.
17. Pillon L, Piccoli A, Lowrie EG, Lazarus JM, Chertow GM. Vector length as a proxy for the adequacy of ultrafiltration in hemodialysis. Kidney Int. 2004;66(3):1266-71.
18. Toso S, Piccoli A, Gusella M, Menon D, Crepaldi G, Bononi A, et al. Bioimpedance vector pattern in cancer patients without disease versus locally advanced or disseminated disease. Nutrition. 2003;19(6):510-4.
19. Nwosu AC, Morris L, Mayland C, Mason S, Pettitt A, Ellershaw J. Longitudinal bioimpedance assessments to evaluate hydration in POEMS syndrome. BMJ Support Palliat Care. 2016;6:369-72. Epub 2016/04/30. doi: 10.1136/bmjspcare-2015-000991. PubMed PMID: 27125269.
20. Toso S, Piccoli A, Gusella M, Menon D, Bononi A, Crepaldi G, et al. Altered tissue electric properties in lung cancer patients as detected by bioelectric impedance vector analysis. Nutrition. 2000;16(2):120-4.
21. Malecka-Massalska T, Smolen A, Zubrzycki J, Lupa-Zatwarnicka K, Morshed K. Bioimpedance vector pattern in head and neck squamous cell carcinoma. JPhysiol Pharmacol. 2012;63(1):101-4.
22. Nwosu AC, Mayland CR, Mason S, Cox TF, Varro A, Ellershaw J. The Association of Hydration Status with Physical Signs, Symptoms and Survival in Advanced Cancer-The Use of Bioelectrical Impedance Vector Analysis (BIVA) Technology to Evaluate Fluid Volume in Palliative Care: An Observational Study. PloS one. 2016;11(9):e0163114. Epub 2016/09/28. doi: 10.1371/journal.pone.0163114. PubMed PMID: 27673684.
23. Piccoli A, Pillon L, Dumler F. Impedance vector distribution by sex, race, body mass index, and age in the United States: standard reference intervals as bivariate Z scores. Nutrition. 2002;18(2):153-67.
24. Piccoli A, Nigrelli S, Caberlotto A, Bottazzo S, Rossi B, Pillon L, et al. Bivariate normal values of the bioelectrical impedance vector in adult and elderly populations. AmJClinNutr. 1995;61(2):269-70.

25. Piccoli A, Pastori G. BIVA software. Department of Medical and Surgical Sciences. University of Padova, Padova, Italy.; 2002.
26. Leard Statistics. Standard Score https://statistics.laerd.com/statistical-guides/standard-score.php2013 [cited 2018 28th March]. Available from: https://statistics.laerd.com/statistical-guides/standard-score.php.
27. Urdan TC. Statistics in Plain English: Lawrence Erlbaum Associates; 2005.
28. Lundberg M, Nikander P, Tuomainen K, Orell-Kotikangas H, Makitie A. Bioelectrical impedance analysis of head and neck cancer patients at presentation. Acta oto-laryngologica. 2017;137(4):417-20. Epub 2017/01/13. doi: 10.1080/00016489.2016.1266510. PubMed PMID: 28079435.
29. Gnagnarella P, Draga D, Baggi F, Simoncini MC, Sabbatini A, Mazzocco K, et al. Promoting weight loss through diet and exercise in overweight or obese breast cancer survivors (InForma): study protocol for a randomized controlled trial. Trials. 2016;17:363. Epub 2016/07/29. doi: 10.1186/s13063-016-1487-x. PubMed PMID: 27464488; PubMed Central PMCID: PMCPMC4963992.
30. Malecka-Massalska T, Chara K, Smolen A, Kurylcio A, Polkowski W, Lupa-Zatwarnicka K. Bioimpedance vector pattern in women with breast cancer detected by bioelectric impedance vector analysis. Preliminary observations. Annals of agricultural and environmental medicine : AAEM. 2012;19(4):697-700. Epub 2013/01/15. PubMed PMID: 23311792.
31. Malecka-Massalska T, Chara K, Golebiowski P, Wladysiuk M, Smolen A, Kurylcio A, et al. Altered tissue electrical properties in women with breast cancer--preliminary observations. Annals of agricultural and environmental medicine : AAEM. 2013;20(3):523-7. Epub 2013/09/28. PubMed PMID: 24069858.
32. Malecka-Massalska T, Smolen A, Morshed K. Body composition analysis in head and neck squamous cell carcinoma. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. 2014;271(10):2775-9. Epub 2013/11/23. doi: 10.1007/s00405-013-2815-3. PubMed PMID: 24264763; PubMed Central PMCID: PMCPMC4149876.
33. Malecka-Massalska T, Smolen A, Morshed K. Body composition analysis in head and neck squamous cell carcinoma. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. 2013. Epub 2013/11/23. doi: 10.1007/s00405-013-2815-3. PubMed PMID: 24264763.
34. Cardoso ICR, Aredes MA, Chaves GV. Applicability of the direct parameters of bioelectrical impedance in assessing nutritional status and surgical complications of women

with gynecological cancer. Eur J Clin Nutr. 2017. Epub 2017/08/10. doi: 10.1038/ejcn.2017.115. PubMed PMID: 28792014.

35. Malecka-Massalska T, Smolen A, Zubrzycki J, Lupa-Zatwarnicka K, Morshed K. Bioimpedance vector pattern in head and neck squamous cell carcinoma. Journal of physiology and pharmacology : an official journal of the Polish Physiological Society. 2012;63(1):101-4. Epub 2012/03/31. PubMed PMID: 22460467.

36. Warnold I, Lundholm K, Scherstén T. Energy Balance and Body Composition in Cancer Patients. Cancer Research. 1978;38(6):1801-7.

37. Prado CM, Maia YL, Ormsbee M, Sawyer MB, Baracos VE. Assessment of nutritional status in cancer--the relationship between body composition and pharmacokinetics. Anti-cancer agents in medicinal chemistry. 2013;13(8):1197-203. Epub 2013/08/08. PubMed PMID: 23919745.

38. Steenson J, Vivanti A, Isenring E. Inter-rater reliability of the Subjective Global Assessment: a systematic literature review. Nutrition. 2013;29(1):350-2. Epub 2012/11/28. doi: 10.1016/j.nut.2012.05.006. PubMed PMID: 23182379.

39. Cederholm T, Bosaeus I, Barazzoni R, Bauer J, Van Gossum A, Klek S, et al. Diagnostic criteria for malnutrition - An ESPEN Consensus Statement. Clin Nutr. 2015;34(3):335-40. Epub 2015/03/24. doi: 10.1016/j.clnu.2015.03.001. PubMed PMID: 25799486.

40. Johnson KS. Racial and Ethnic Disparities in Palliative Care. Journal of Palliative Medicine. 2013;16(11):1329-34. doi: 10.1089/jpm.2013.9468. PubMed PMID: PMC3822363.

41. Martinoli R, Mohamed EI, Maiolo C, Cianci R, Denoth F, Salvadori S, et al. Total body water estimation using bioelectrical impedance: a meta-analysis of the data available in the literature. Acta Diabetol. 2003;40 Suppl 1:S203-6. Epub 2003/11/18. doi: 10.1007/s00592-003-0066-2. PubMed PMID: 14618473.

42. Guyton A, Hall J. Textbook of Medical Physiology. Tenth edition ed: W.B Saunders Company; 2000.

43. Demark-Wahnefried W, Peterson BL, Winer EP, Marks L, Aziz N, Marcom PK, et al. Changes in Weight, Body Composition, and Factors Influencing Energy Balance Among Premenopausal Breast Cancer Patients Receiving Adjuvant Chemotherapy. Journal of Clinical Oncology. 2001;19(9):2381-9. doi: 10.1200/JCO.2001.19.9.2381.

44. Mourtzakis M, Prado CMM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Applied Physiology, Nutrition, and Metabolism. 2008;33(5):997-1006. doi: 10.1139/H08-075.

45. Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Manuel Gomez J, et al. Bioelectrical impedance analysis-part II: utilization in clinical practice. Clin Nutr.

2004;23(6):1430-53. Epub 2004/11/24. doi: 10.1016/j.clnu.2004.09.012. PubMed PMID: 15556267.

46. Lentner C. Introduction to statistics. Statistical tables. Mathematical formulae. In: Geigy scientific tables. 8 ed: Basel: Ciba-Geigy Limited; 1982. 1 p.

47. Jolicoeur P. Introduction to biometry: New York: Kluwer Academic/Plenum Publishers; 1999.

48. Harris EK, Boyd, J.C.,. Statistical bases of reference values in laboratory medicine: New York: Marcel Dekker; 1995.

49. Mardia KV, Kent JT, Bibby JM. Multivariate analysis: Academic Press; 1979.

50. Morrison DF. Multivariate statistical methods: Thomson/Brooks/Cole; 2005.

51. Rösler A, Lehmann F, Krause T, Wirth R, von Renteln-Kruse W. Nutritional and hydration status in elderly subjects: Clinical rating versus bioimpedance analysis. Archives of Gerontology and Geriatrics. 2010;50(3):e81-e5. doi: http://dx.doi.org/10.1016/j.archger.2009.06.007.

52. Lukaski HC, Bolonchuk WW, Siders WA, Hall CB. Body composition assessment of athletes using bioelectrical impedance measurements. JSports MedPhysFitness. 1990;30(4):434-40.

53. Piccoli A, Brunani A, Savia G, Pillon L, Favaro E, Berselli ME, et al. Discriminating between body fat and fluid changes in the obese adult using bioimpedance vector analysis. IntJObesRelat Metab Disord. 1998;22(2):97-104.

54. Ott M, Lembcke B, Fischer H, Jager R, Polat H, Geier H, et al. Early changes of body composition in human immunodeficiency virus-infected patients: tetrapolar body impedance analysis indicates significant malnutrition. AmJClinNutr. 1993;57(1):15-9.

55. Scalfi L, Di Biase G, Coltorti A, Contaldo F. Bioimpedance analysis and resting energy expenditure in undernourished and refed anorectic patients. Eur J Clin Nutr. 1993;47(1):61-7. Epub 1993/01/01. PubMed PMID: 8422874.

56. Piccoli A, Piazza P, Noventa D, Pillon L, Zaccaria M. A new method for monitoring hydration at high altitude by bioimpedance analysis. MedSciSports Exerc. 1996;28(12):1517-22.

57. Piccoli A. Identification of operational clues to dry weight prescription in hemodialysis using bioimpedance vector analysis. The Italian Hemodialysis-Bioelectrical Impedance Analysis (HD-BIA) Study Group. Kidney Int. 1998;53(4):1036-43. Epub 1998/04/29. doi: 10.1111/j.1523-1755.1998.00843.x. PubMed PMID: 9551415.

Appendix

Formulas for the calculation of the bio-impedance confidence and tolerance ellipses

The following section has been adapted (with permission) from Piccoli A , Pastori: BIVA software.[25]

Geometrical parameters for drawing the RXc Graph and the RXc-score Graph

Confidence and tolerance intervals can be calculated for the bivariate normal distribution.[46-50] A simple linear correlation analysis can be used for calculation following appropriate modification of the equations.[9, 23]

Given n pairs of observations x and y, with standard deviation s_x and s_y, and correlation coefficient r, for a fixed α probability level, the Snedecor's F_α value is taken with 2 and n-2 degrees of freedom.

RXc Graph

The RXc graph semi-axes (L_1 and $L_{2)}$ and the slopes (b_1 and $b_2 = -1/b_{1)}$, of the axes of the 100(1-α)% confidence and tolerance ellipses (e.g. α= 0.05, 0.25, and 0.50 for the 95th, 75th, and 50th percentile, respectively) can be calculated using the equations 2a and 3a, respectively.

RXc-score graph

The parameters of tolerance ellipses of bivariate Z-scores (RXc Zscore graph) can be calculated accordingly, using equations 1b and 2b.[23]

Equation 1 a

$$\mathbf{L1, L2} =$$

$$\sqrt{\boldsymbol{K}}.\sqrt{(n-1)\left(s_{x^2}+\ x_{y^2}\right) \pm \sqrt{\left[(n-1)(s_{x^2}+s_{y^2})\right]^2 - 4\ (n-1)^2(1-r^2)s_{x^2}\ s_{y^2}}}$$

Equation 1 b

$$\boldsymbol{L1, L2} = \sqrt{\boldsymbol{K}}.\ \sqrt{\mathbf{2}\ (\boldsymbol{n}-\mathbf{1}) \pm \mathbf{2}\ \boldsymbol{r}\ (\boldsymbol{n}-\mathbf{1})}$$

Where

K = F/n·(n-2) for confidence ellipses

K = F·(n+1)/n·(n-2) for tolerance ellipses

Equation 2 a

$$\boldsymbol{b_1, b_2} = \left(\boldsymbol{b}, -\frac{\mathbf{1}}{\boldsymbol{b}}\right) = (\boldsymbol{s_{y^2}} - \boldsymbol{s_{x^2}})/\mathbf{2}\boldsymbol{r}\boldsymbol{s_x}\boldsymbol{s_y} \pm \sqrt{\mathbf{1} + \left[(\boldsymbol{s_{y^2}} - \boldsymbol{s_{x^2}})/\mathbf{2}\ \boldsymbol{r}\boldsymbol{s_x}\boldsymbol{s_y}\right]^2}$$

Equation 2b

$$\boldsymbol{b_1, b_2} = \pm\mathbf{1}$$

Figure and Table Legends

Table 1 Details of the studies included in the BIVA RXc z-score analysis

Key	Author	Characteristics	N	Mean age (years)	Gender	BMI (kg/m^2)	Tolerance	Body composition	Analyser
●	Nwosu 2016[22]	Mixed cancer Males (n=42) mean age 70.6 (SD 11.0), median 71.0) BMI 26.4 (SD 5.2) predominantly Caucasian, advanced cancer with different disease types. United Kingdom.	42	70.60	Male	26.4	50%	Normal	Analyzer The EFG3 ElectroFluidGraph Vector Impedance Analyser (Akern)
▲	Nwosu 2016[22]	Mixed cancer Female (n=48) mean age 71.6 (SD 13.3), median 74, BMI 24.1 (4.7) predominantly Caucasian, with different disease types. United Kingdom.	48	76.10	Female	24.1	50%	Normal	Analyzer The EFG3 ElectroFluidGraph Vector Impedance Analyser (Akern)
■	Toso 2000[20]	lung cancer stage IIIB Males, n=33. Mean age 67 (SD 5.0), BMI 25 (SD 5.5) Caucasian, lung cancer stage IIIB. Italy.	33	67.00	Male	25.0	50%	Normal	Analyzer BIA-101, RJL/Akern Systems, Clinton Town- ship, MI, USA

○	Toso 2000[20]	lung cancer stage IV Males, n=30, mean age 64 (SD 7.0), BMI 25 (SD 3.1) Caucasian, lung cancer stage IV, Italy.	30	64.00	Male	25.0	75%	Cachexia	Analyzer BIA-101, RJL/Akern Systems, Clinton Town- ship, MI, USA
△	Malecka-Massalska 2012[30] 2013[31]	Breast cancer Females, n=34, mean age =53.88 (SD 10.84) breast cancer (n=34) Poland.	61	53.88	Female	-	95%	Athletic	Analyzer ImpediMed bioimpedance analysis SFB7 BioImp v1.55, Queensland, Australia.
□	Malecka-Massalska 2012[21] 2014 [32]	Head and neck cancer Males, n=28, mean age 57.1 (SD 7.3), BMI 22.8 (5.0), Caucasian, head and neck cancer.	34	57.10	Male	-	95%	Cachexia	Analyzer ImpediMed bioimpedance analysis SFB7 BioImp v1.55, Queensland, Australia.
	Toso 2003[18]	Lung cancer Males, n=61, mean age =66 (SD 6), BMI= 25 (SD 4), Caucasian, lung cancer, locally advanced and disseminated.	56	66.00	Male	25.0	75%	Cachexia	Analyzer BIA-101, RJL/Akern Systems, Clinton Township, MI, USA
X	Toso 2003[18]	Lung cancer in remission Males, n=31, mean age= 63 (SD 10), BMI= 25 (SD 4) Caucasian, lung cancer in remission (n=31)	31	63.00	Male	25.0	50%	Normal	Analyzer BIA-101, RJL/Akern Systems, Clinton Township, MI, USA
◊	Melecka-	Head and neck cancer	67	67.00	Male	22.9	75%	Cachexia	Analyzer

	Massalska 2013[33]	Males, Caucasian n=67, mean age = 56.8 (SD 7.9), BMI 22.9 (SD 4.4), Caucasian, head and neck cancer, Poland.							ImpediMed bioimpedance analysis SFB7 BioImp v1.55, Queensland, Australia.
*	Cardoso 2017[34]	Gynaecological cancer Female, n=208, mean age= 60 (range 51-67), BMI = underweight (12(6%), normal 52(25%), overweight 55 (26%), obese 89 (43%). White n=89(43%), mixed races 92(42%), Black 26(13%). Gynaecological cancer. Brazil	208	60.00	Female	-	50%	Normal	BIA 450 Bioimpedance Analyzer, Biodynamics, Shoreline, WA, USA

509

510 *RXc z score data analysed with BIVA software using equations included in the appendix.*

511

512 **Table 2: Bioimpedance Z score data for the included studies**

Study details	R/H (Ohm/m)	Xc/H (Ohm/m)	Reference population data*					Z(R) score	Z(Xc) score
			N	R/H (Ohm/m) mean	R/H (Ohm/m) SD	Xc/H (Ohm/m) Mean	Xc/H (Ohm/m) SD		

Males, mixed cancer - Nwosu 2016[22]	306.6	26.1	354	371.9	43.2	30.8	7.2	0.19	-0.65
Females, mixed cancer - Nwosu 2016[22]	372.2	29.1	372	298.6	49.0	34.4	7.7	0.01	-0.69
Males, White, Lung cancer stage IIIB, - Toso 2000[20]	302.0	25.0	354	371.9	43.2	30.8	7.2	0.08	-0.81
Males, White, Lung cancer stage IV, - Toso 2000[20]	314.0	24.0	354	371.9	43.2	30.8	7.2	0.36	-0.94
Females with breast cancer - Malecka-Massalska 2012[30] 2013[31]	377.54	53.58	372	298.6	49.0	34.4	7.7	0.12	2.49
Males with head and neck cancer- Melecka-Massalska 2013[33]	342.54	27.62	354	371.9	43.2	30.8	7.2	1.02	-0.44
Males with lung cancer locally advanced and disseminated - Toso 2003[18]	317	26.0	354	371.9	43.2	30.8	7.2	0.43	-0.67
Males with lung cancer in remission - Toso 2003[18]	287	25.0	354	371.9	43.2	30.8	7.2	-0.27	-0.81
Males with head and neck cancer - Melecka-Massalska 2013[33]	327.01	28.04	354	371.9	43.2	30.8	7.2	0.66	-0.38
Females (mixed race) gynaecological cancer - Cardoso 2017[34]	349.8	34.4	372	298.6	49.0	34.4	7.7	-0.45	0.00

513 **The Piccoli et al 1995[24] reference population data was used for all studies included in this analysis. BIVA software equations are included in*

514 *the appendix.*

515

516

Figure 1: The RXc graph with 95%, 75% and 50% tolerance ellipses. Reproduced and modified with permission.[51]

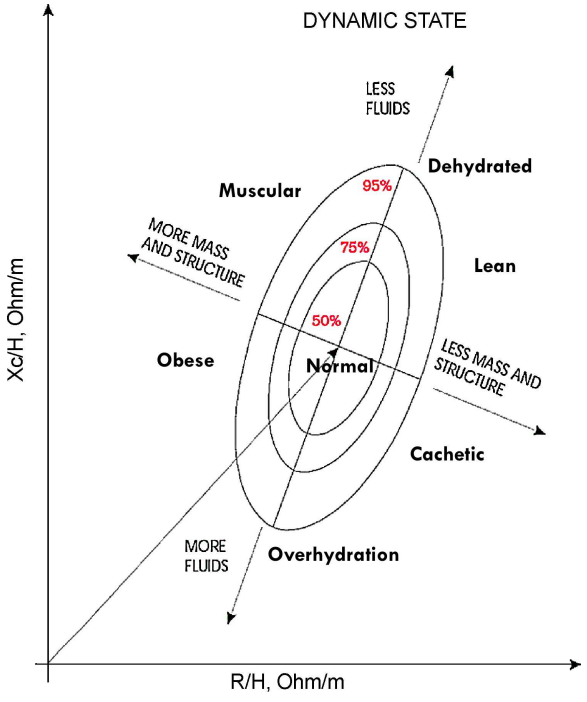
Figure 2: **The BIVA z-score graph: data drawn from the literature and plotted on the RXc z-score graph after transformation of the impedance measurements from several disease groups into bivariate z-scores (with respect to their reference population). Modified with permission.[23]**

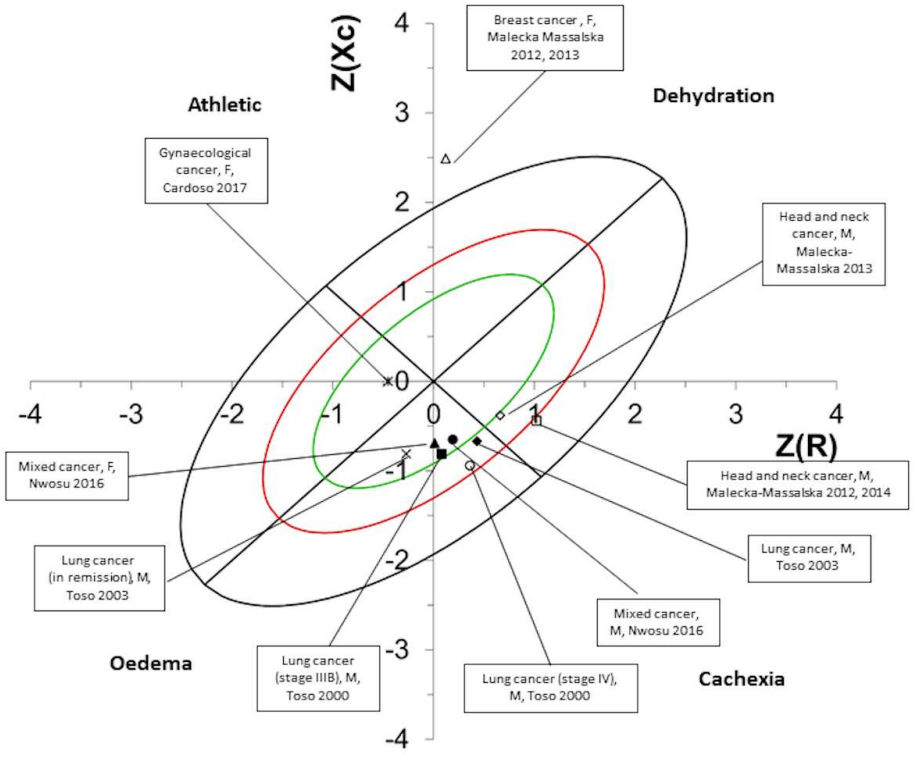
Solid and open circles represent male and female, respectively. A forward or backward displacement of vectors parallel to the major axis of ellipses was associated with dehydration or fluid overloading, respectively, reaching extremes out of the poles. Single score vectors are from athletes,[52] obese subjects of class I to III[53] or patients with chronic renal failure in conservative treatment, nephrotic syndrome (oedema), lung cancer,[20] acquired immunodeficiency syndrome in stages WR 3 to 5 or WR 6,[54] and anorexia nervosa.[55] Repeated score vectors are from climbers before and after high altitude dehydration,[56] Haemodialysis patients, either lean[57] or obese,[53] before and after fluid removal with a dialysis session, and dehydrated patients with cholera before and after fluid infusion.[12] Vectors above or below the major axis (meaning upper left or lower right half of ellipses) were associated with more or less cell mass in soft tissues, respectively, with extremes along the minor axis. Abbreviations: CRF = chronic renal failure; HD= haemodialysis; HDo= obese haemodialysis patients; HIV= human immunodeficiency virus stages 1-6; Ob/1-3= obese subjects of classes I to III; WR= Walter Reed stages 1-6. Reproduced with permission.[23]

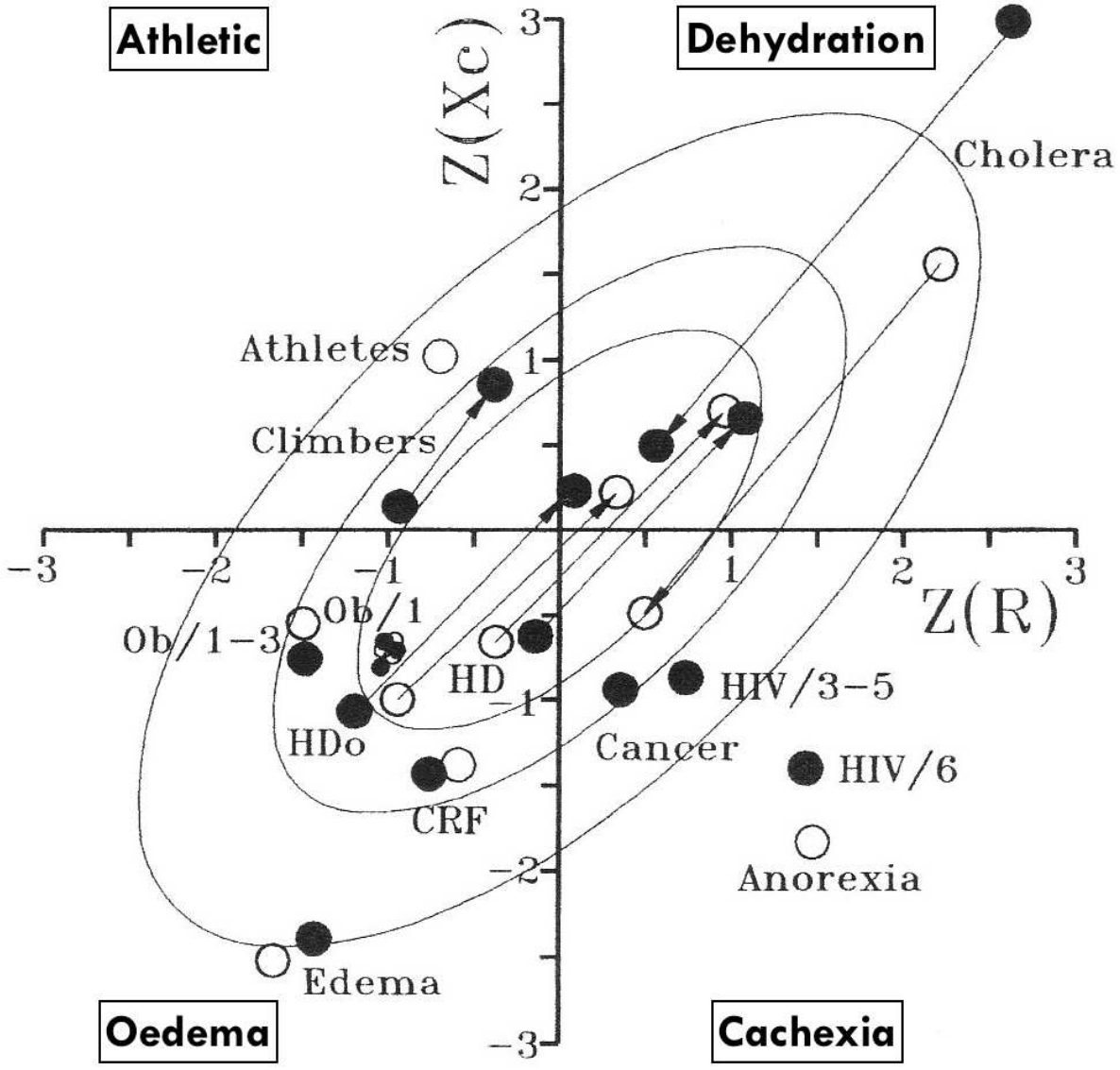
Figure 3: Overall selection process for clinical studies included in the BIVA Z score analysis

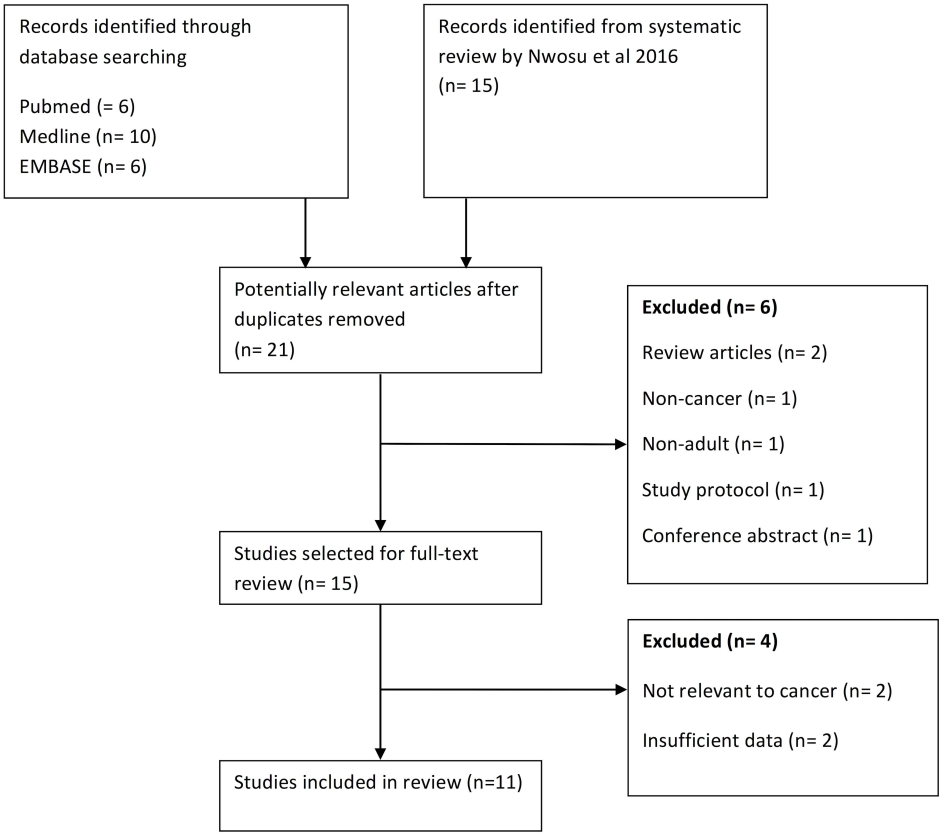
Figure 4: RXc z-score graph analysis of bioelectrical impedance vector analysis (BIVA) data from studies of patients with cancer.

Data drawn from the literature and plotted on the RXc-score graph after transformation of impedance measurements from several disease groups into bivariate Z scores (with respect to the Piccoli 1995 reference population[24]). Further details of the equations used for the analysis are available in the appendix.




Z(Xc)
Z(R)
Athletic
Dehydration
Oedema
Cachexia
Breast cancer , F, Malecka Massalska 2012, 2013
Gynaecological cancer, F, Cardoso 2017
Head and neck cancer, M, Malecka-Massalska 2013
Mixed cancer, F, Nwosu 2016
Head and neck cancer, M, Malecka-Massalska 2012, 2014
Lung cancer, M, Toso 2003
Lung cancer (in remission), M, Toso 2003
Mixed cancer, M, Nwosu 2016
Lung cancer (stage IIIB), M, Toso 2000
Lung cancer (stage IV), M, Toso 2000


Athletic
Dehydration
Oedema
Cachexia
Z(Xc)
Z(R)
3
2
1
−1
−2
−3
−3
−2
−1
1
2
3
Cholera
Athletes
Climbers
Ob/1
Ob/1−3
HD
HDo
HIV/3−5
Cancer
HIV/6
CRF
Anorexia
Edema



Author Contribution Statement

The author's responsibilities were as follows.

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Statistical analysis: ACN, TFC

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