Correlation and principal component analysis of clinical, bioelectrical and functional variables in newly diagnosed lung cancer adult patients. Pilot study

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Research Article

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Correlation and principal component analysis of clinical, bioelectrical and functional variables in newly diagnosed lung cancer adult patients: Pilot study

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Abstract

Background: Bioelectrical impedance analysis has been used in cancer patients. The aim of this study is to propose an integrated analysis of clinical, bioelectrical and functional variables in newly diagnosed lung cancer adult patients for the integral evaluation and possible prognostic of them.

Methods: This Pilot study was retrospective and cross-sectional and 23 patients aged 53-82 years participated in it. The electrical resistance and capacitive electrical reactance were measured with the Bodystat Quadscan® 4000 analyzer. The electrical impedance modulus and the phase angle were calculated. The serum concentrations of epidermal growth factor, CYFRA21-1 and CA 72-4 were quantified. Correlations/associations among variables and the principal component analysis were suggested.

Results: The majority of patients had tumor markers, electrical resistance and the phase angle in their respective normal ranges. The capacitive electrical resistance was below its normal range. Minimum, low and moderate grades of linear correlation/association prevailed among studied variables. The principal components I and II were interpreted as prognosis and body energetic reserve of the patient, respectively.

Conclusions: It is concluded that the clinical, bioelectrical and functional variables allow the integral analysis and possible prognosis of newly diagnosed lung cancer adult patients. The decrease of the capacitive electrical reactance is the most influence to the loss of the body energetic reserve that leads to alterations of the overall health, tiredness and decrease of weight and body mass index of these patients.

Key words: Bioelectrical impedance analysis, newly diagnosed lung cancer adult patients, Spearman's Rho correlation coefficient, association coefficient of eta, principal component analysis

Background

Lung cancer is a common disease in adult patients; main cause of death of all malignant tumor types; second cause of death of all types of death worldwide; and its diagnostic techniques are expensive, invasive, not applicable to several patients, and not fully confirmatory for the diagnosis and prognosis of lung cancer adult patients, LCAPs [1]. High concentrations in blood serum of Epidermal Growth Factor (sEGF), monoclonal antibody that recognizes a fragment of cytokeratin 19 (sCYFRA21-1), and glycoprotein TAG-72 (sCA 72- 4) tumor markers may be indicators of tumor malignancy degree and poor prognosis [2, 3]. In addition, ECOG (Eastern Cooperative Oncology Group) functional scales, named ECOG-fs, allow objectifying the quality of life of cancer patients [1].

Body hydration state, body cell mass, prognosis, survival and quality of life of LCAPs, sick patients and apparently healthy adult subjects (AHASs) have been related to different bioelectrical variables (BBVs), as electrical resistance, R, capacitive electrical reactance, Xc, electrical impedance modulus, $|Z|$, and phase angle, θ [4-7]. Short survival is observed in LCAPs for $\theta \leq 4.5^{o}$ [4, 8]. Other BBVs (e.g., R/H, Xc/H, H^2/R and H^2/Xc) have been used too, where H is the height of the subject [4-9].

We are not aware of an integrated study involving correlation and Principal Component Analysis (PCA) of patient biological variables (PBVs), tumor biological variables (TBVs), and BBVs in LCAPs. Therefore, the aim of this study is to propose an

integrated analysis of PBVs, TBVs and BBVs in newly diagnosed lung cancer adult patients (NDLCAPs).

Methods

Ethic aspects

This retrospective cross-sectional Pilot study was carried out at the Pneumology Service of the hospital General Santiago Dr. Juan Bruno Zayas Alfonso, Santiago de Cuba, Cuba (from March 1 to September 30, 2018). It was approved by the Ethics Committee (108823SC900-149, May 5, 2017) and the Scientific Council (Resolution 189/2017) of this hospital, governed by the ethical standards of the Declaration of the Helsinki World Medical Assembly, [10] and fulfilled with good medical clinical practices established by the Ministry of Health of the Republic of Cuba [11].

NDLCAPs were included in this research once they, companion and witness (psychologist) proceeded to the reading, agreed, and signed the Informed Consent. They received previously a detailed explanation of objectives, importance and purposes of this study, and requirements established for measurements (empty bladder, no smoking at least 24 h prior, no intake of steroids at least one week before, no intake of alcoholic beverages at least 24 h prior, fasting 2 h minimum, and non-performance of physical exercises 12 h before taking measurements) [7].

Patients

The inclusion criteria were the Informed Consent, lung cancer cyto-histological diagnosis and the patient received medical attention at the Pneumology Service.

Exclusion criteria were patient and/or family refusals to participate in this study, patients with metallic implants in the body, amputated limbs, generalized skin diseases,

serious infections, and disorders of body fluids. Voluntary abandonment and death were established as exit criteria. Measurements were conducted to 23 NDLCAPs aged 53-82 years (14 men and 9 women) with different tumor histological varieties. A numerical code (from 1 to 23) was assigned to each patient in order of arrival.

Variables

The personal history of each patient was collected and 11 original independent variables were reported: six PBVs (H, age, body weight, gender, body mass index (BMI), and degree of the ECOG-fs (d-ECOG-fs); two TBVs (lung cancer stage (LCS) and lung cancer histological variety (LCHV)), and three BBVs (R, Xc and θ). Furthermore, R/H, Xc/H, R/H^2 and Xc/H^2 variables were analyzed. All these variables were quantitative, except categorical variables (gender, d-ECOG-fs and LCHV). The number 1 was assigned to the male gender (M) and the number 2 to the female gender (F). The numbers 1, 2, 3, 4 and 5 were allocated to LCHV small cell, large cell, squamous cell carcinoma, adenocarcinoma, and non-small cell carcinoma, respectively.

BMI was calculated for each one of NDLCAPs from the weight/H^2 ratio (weight (in kg), H (in m)). LCHV was confirmed by pathological anatomy. TNM staging of the lung cancer was reported by the American Joint Committee on Cancer [12].

Furthermore, the relative change in unintentional body weight of each NDLCAPs (ΔP, in %) was calculated by means of $\Delta P \cong \left[(P_o - P_e)/P_e\right]100\,\%$, where P_e was the expected patient weight if he did not have cancer (estimated from the reference Table of body weight for AHASs by H, gender and age group) and P_o his measured body weight.

Three degrees for the decrease in ΔP (ΔP < 0) were established: slight ($|\Delta P| \leq 5$ %), moderate ($5 < |\Delta P| \leq 10$ %) and severe ($|\Delta P| > 10$ %) [13]. d-ECOGs-fs were 0, 1, 2, 3, 4, or 5 (1, 13). Grade 5 was not considered because no patient died during measurements.

Measurement of sEGF, CYFRA21-1 and CA 72-4 tumor biomarkers

The basal concentration of sEGF (in pg/ml) was quantified with the Ultra Micro Analytical System technology (SUMA®, Centro de InmunoEnsayo (BioCubaFarma) La Habana, Cuba). Basal concentrations of sCYFRA 21-1 (in ng/mL) and sCA 72-4 (in U/mL) were quantified with the Lecto Ultra Micro Analytical System technology (LECTO-SUMA®, Centro de InmunoEnsayo). Both technologies are located in the SUMA Laboratory of the hospital General Santiago Dr. Juan Bruno Zayas Alfonso. sEGF measurement was made with UMELISA-EGF® diagnostic technique (UMELISA-EGF® reagent kit was produced and supplied by the Centro de InmunoEnsayo). sCYFRA 21-1 and sCA 72-4 measurements were made with the Elecsys diagnostic technique (Elecsys reagent kit was produced and supplied by the Centro de InmunoEnsayo, ECLISA®).

It was extracted 5 mL of blood to each one of NDLCAPs. For sEGF, a fraction of this blood was placed in a dry tube and allowed to stand for 4 h to obtain the serum. Samples were stored at -20 ºC. The serum in aliquots of 500 µL was preserved to facilitate its subsequent use. Additionally, sEGF concentration of each patient was referred to that of AHASs, by each gender and age group [14]. For sCYFRA 21-1 and sCA 72-4, the other fraction of 5 mL of blood was placed in a standard sample tube and left to stand for 2 h to obtain the serum. Samples were stored between 2 and 8 ºC. sCYFRA 21-1 and sCA 72-4 concentrations were referred to their respective normal ranges 0.1 - 3.30 ng/mL and 0.1 - 6.90 U/mL, respectively [2]. Each sample was identified with the patient code and the date of collection. In addition, the estrogen receptor was not quantified because none of NDLCAPs had breast cancer previously.

Electric bioimpedance analyzer

The Bodystat Quadscan® 4000 multi-frequency analyzer (company Bodystat, LTD, Douglas Isle of Man, British Isles, available at https://www.bodystat.com/) was used to estimate R and Xc values. |Z| ($|Z| = \sqrt{R^2 + Xc^2}$) and θ ($\theta = tg^{-1}(Xc/R)$) were calculated. As |Z| - R ≤ 3.0 Ω (difference that had not statistical significance or in clinics), it was presumed that $|Z| \cong R$ [7]. Consequently, we assume that $R = H/\sigma S$ and therefore $R/H = 1/\sigma S$ and $R/H^2 = 1/\sigma S$, where σ, S, and V were the body electrical conductivity, conductor cross section, and conductor volume of each one of NDLCAPs, respectively. This device operated at frequencies of 5, 50, 100 and 200 kHz; nevertheless, all BBVs were reported at 50 kHz. The calibrator supplied by the manufacturer (500.0 ± 0.1 Ω) allowed evaluating the stability of this BIA analyzer at the beginning and the end of the measurement in each patient.

Measurement procedure

The standardized procedure internationally to measure BBVs [4-9] was used in this study. Measurements were carried out in the morning hours (from 8 to 9 am) by a trained nurse. Before that, the measurement of the H to the nearest 0.5 cm was conducted using the technique of the International Biological Program with the head located in the Frankfort plane. The precision of this technique was ± 0.1 cm. Body weight was measured with a Soehnle Professional digital scale (model 2755, Soehnle Industrial Solution, Backnany, Germany) with an accuracy of ± 0.5 kg. Measurements were made under controlled environmental conditions: temperature of 25 ± 1 ºC (Sattigungs thermometer of precision ± 1 ºC, Germany), a relative humidity of 60 ± 5 % (Fischer Polymeter of precision ± 1 %, Germany) and a neutral environment (free of field generating equipment and electromagnetic radiation).

The patients were covered with light clothing and placed in a supine position on a non-conductor surface, without a pillow under the head, with the arms separated at approximately 30° from the thorax and the legs separated approximately at an angle of 45° without contact between them. The skin of each patient was first cleaned with water and soap, and then 70 % alcohol to ensure asepsis of the areas where the electrodes were attached.

The right tetrapolar ipsilateral method was used. The stimulating electrodes (or injection electrodes of alternating electric current) were placed in the medial areas of the dorsal surfaces of hands and feet, near the metacarpal and metatarsal phalangeal joints, respectively. The sensing electrodes (or receiving electrodes the body electrical voltage) were placed between the distal epiphyses of the radius and the ulna, at the level of the pisiform eminence, as well as at the midpoint between both malleoli, respectively. The distance between the sensing and stimulating electrodes was 5.0 cm and measured with a standard measuring tape (model RT-144, Wintape Measuring Tape Co., Ltd, Guangdong, China) of 0.1 cm precision. Electrocardiogram electrodes (model APR-020, All Pro Corporation Company, Quingdao, China) were used. The material of each electrode was Silver/Silver Chloride (Ag/AgCl).

Comparison between bioelectrical parameters of NDLCAPs and AHASs

Values of R, R/H, R/H^2, Xc, Xc/H, Xc/H^2, and θ were reported individually for each one of NDLCAPs. From these individual values, the mean ± standard deviation (standard error of the mean = standard deviation/ $\sqrt{N}$, where N was the total number of patients) of R/H, Xc/H and θ were calculated and referenced with their respective normal ranges reported for AHASs ($(R/H)_r$, $(Xc/H)_r$, and θ_r) [15], by gender, and age groups 17-59 and 60-80. The standard error of the mean was used in comparisons of

means of R/H with $(R/H)_r$, Xc/H with $(Xc/H)_r$, and θ with θ_r to homogenize the sample by gender and age group due to the biological individuality.

Spearman's rho correlation coefficient

The estimator of Spearman's rank correlation coefficient (r) was used to determine the degree of linear correlation between pairs of variables mentioned above. This linear correlation was significant statistically when $p \leq 0.05$ (significance level). For Medicine, Akoglu [16] suggested open intervals for r but some its values were not included between two contiguous of them. Therefore, we proposed: none ($r = 0.0$), minimal ($0.0 < r \leq 0.2$), low ($0.2< r \leq 0.5$), moderate ($0.5 < r \leq 0.7$), good ($0.7 < r \leq 0.9$), very good ($0.9 <r < 1.0$) and perfect ($r = 1.0$).

Eta correlation coefficient

The eta correlation/association coefficient (η) was calculated from the formula reported by Smith [17]. It was applied to variables that had not linear correlation and allowed to know if there was a curvilinear relationship between them. We suggested ranges for η (in analogy with r): none ($\eta = 0.0$), minimal ($0.0 <\eta \leq 0.2$), low ($0.2 <\eta \leq 0.5$), moderate ($0.5 < \eta \leq 0.7$), good ($0.7 < \eta \leq 0.9$), very good ($0.9 < \eta < 1.0$) and perfect ($\eta = 1.0$).

Principal Components Analysis

We used PCA descriptive statistical technique to reduce the dimensionality and determine the similar groups of variables because an eleven-dimensional graphic (11 independent variables) for the representation of 23 NDLCAPs would be impossible to visualize, as reported Johnstone and Lu [18].

Maximum number of principal components (PCs) was 11 and represented by PCi (i = 1, …, 11), which are linear combinations of 11 original variables. Main PCs that provided more information were selected from the Kaiser criterion (eigenvalues greater than 1). A threshold percentage of 40 % was fixed to select the highest variable weights for each one of PCs chosen. PCs that contributed little information were removed. For this, different graphic strategies were analyzed: 1) outliers graphic chart (distance chart of Mahalonobis versus observation); 2) sedimentation graphic (chart of eigenvalues versus number of components); 3) score graphic (projection chart in the plane of all patients); 4) influence graphic (projection chart in the plane of all variables); 5) double projection graphic (projections of all NDLCAPs and variables in the plane of PCs were simultaneously represented. In these last three graphic were visualized four quadrants: Quadrant I (top right), Quadrant II (top left), Quadrant III (bottom left), and Quadrant IV (bottom right).

These graphical strategies were also showed when the pair (R, Xc) was substituted by the pair (R/H, Xc/H) or (R/H^2, Xc/H^2) in PCA for the same six PBVs, two TBVs and θ. Furthermore, all these variables were labeled for a best presentation of results obtained from correlation (linear and curvilinear) and PCA: age (X_1), gender (X_2), patient weight (X_3), H (X_4), R (X_5), Xc (X_6), θ (X_7), d-ECOG-fs (X_8), tumor stage (X_9), LCHV (X_{10}), BMI (X_{11}), R/H (X_{12}), Xc/H (X_{13}), R/H^2 (X_{14}) and Xc/H^2 (X_{15}).

PCA and r were analyzed in the Minitab® 14 statistical program (Minitab Inc for Windows, 2003, free software, National Institute of Standards and Technology, Pennsylvania State University, USA, https: //www.minitab.com/en-mx/products/minitabs). This program ran on a computer (Department of Mathematics, Universidad de Oriente, Santiago de Cuba, Cuba) with Windows 8 operating system with 2.6 GB RAM; 64 bit, 64 processor, Inter R core tm. The duration of the statistical

processing of the data was approximately 2 s. Data will be kept for 15 years in the Pneumology Service of the hospital General Santiago Dr. Juan Bruno Zayas Alfonso.

Results

Original independent variables

Hypertension was observed in 56.52 % (seven men and six women) of NDLCAPs, and two men and a women ingested diuretics. Dehydration was not clinically observed in NDLCAPs. Cachexia and overweight were observed clinically in three and five NDLCAPs, respectively.

Table 1 showed the code; age; gender; H; P_o; ΔP; d-ECOG-fs; LCHV; LCS; sEGF, sCYFRA 21-1, and sCA 72-4 concentrations; and R, R/H, Xc, Xc/H, and θ values of NDLCAPs. M, age group 60-80 years and adenocarcinoma in 60.87 % prevailed. The M/F ratio was 1.56 (14/9). Stage IV lung cancer (65.22 %, eight men and seven women) and d-ECOG-fs 3 (65.22 %, eight men and seven women) prevailed. Furthermore, $\Delta P > 0$ was observed in 56.52 % (seven men and six women) of NDLCAPs. The rest of patients (43.48 %, seven men and three women) had severe (6), moderate (1) and slight (3) decreases in ΔP.

The mean ± standard error of sEGF, sCYFRA 21-1 and sCA 72-4 concentrations for NDLCAPs and AHASs were shown in Table 2 for each age group and gender. Low average sEGF (except for females of the 46 to 60 age group) and high sCYFRA 21-1 in NDLCAPs were observed respect to those for AHASs by each age group and gender. Majority of NDLCAPs had normal concentrations of these three biomarkers. Nevertheless, some patients had sEGF (26.09 %), sCYFRA 21 (43.48 %) and sCA 72-4 (34.78 %) concentrations increased.

Table 3 showed the mean ± standard deviation (standard error of the mean) of R/H, Xc/H and θ (for NDLCAPs), and $(R/H)_r$, $(Xc/H)_r$ and θ_r (for AHASs) by age group and gender. Women AHASs, women had higher values of $(R/H)_r$ and $(Xc/H)_r$ and lower values of θ_r than men AHASs for each age group, being noTable for the 17 to 59 age group. Furthermore, men and women of the 60 to 80 age group showed higher values of $(R/H)_r$, and lower values of $(Xc/H)_r$ and θ_r than those of the 17 to 59 age group for each gender. For both age groups, female NDLCAPs showed lower R/H, Xc/H, and θ average values than those of female AHASs, whereas men NDLCAPs had higher R/H average values, a slight decrease of their Xc/H and θ average values than those of men AHASs. Female patients showed R/H and θ values lower than those of male patients for the 17 to 59 age group, not for the 60 to 80 age group. Female patients showed an increase in Xc/H compared to men patients of both age groups. Furthermore, R/H and Xc/H values of male and female patients of the 17 to 59 age group were smaller than their respective values in the 60 to 80 age group for both genders. Male patients in the 17 to 59 age group had higher value of θ than those the 60 to 80 age group. Nevertheless, it was similar in female patients of both age groups.

Respect to $(R/H)_r$, $(Xc/H)_r$ and θ_r, R/H values were distributed below (39.13 %), above (8.70 %) and in the normal range (52.17 %); Xc/H values were concentrated below (60.87 %), above (4.35 %) and in the normal range (34.78 %). 21.74, 21.74 and 56.22 % of θ values had below, above and in the normal range, respectively. For male patients, R/H values were grouped below (35.71 %), above (14.29 %) and in the normal range (50.00 %); 64.29, 7.14 and 28.57 % of them had their Xc/H values below, above and in the normal range, respectively; and θ values had below (14.29 %), above (7.14 %) and in the normal range (78.57 %). For female patients, R/H values were congregated below (44.44 %) and in the normal range (55.56 %); Xc/H values were concentrated below

(55.56 %) and in the normal range (44.44 %); and 33.33, 44.44 and 22.23 % of θ values had below, above and in the normal range, respectively. Cachectic and overweight had their R/H values in the normal range, whereas Xc/H and θ values were distributed outside their respective normal ranges (Table 3).

Spearman's rank correlation coefficient

Table 4 showed the estimator of r and its associated probability p (in brackets) for each pair of independent variables. H had a linear, good and negative correlation with gender; and linear, moderate and positive correlation with P_o. The gender and R had a linear, low and positive correlation. Xc had a linear, low and negative correlation with age. The d-ECOG-fs had a linear, low and positive correlation with gender; and linear, low and negative correlations with P_o and H. BMI and P_o had a linear, good and positive correlation.

The R/H had a linear, moderate and positive correlation with gender; linear, moderate and negative correlation with H; linear, good and positive correlation with R; and linear, low and positive correlation with d-ECOG-fs. Xc/H had linear, low and positive correlations with gender and R; linear, moderate and positive correlation with R/H; and linear, good and positive correlation with Xc. Furthermore, R/H^2 had linear, good and positive correlations with gender and R; linear, good and negative correlation with H; linear, very good and positive correlation with R/H; linear, moderate and positive correlation with Xc/H; and linear, low and positive correlation with d-ECOG-fs. Additionally, Xc/H^2 had a linear, very good and positive correlation with Xc/H; linear, good and positive with Xc; linear, moderate and positive correlations with gender, R/H and R/H^2; linear, moderate and negative correlation with T; and linear, low and positive

correlation with R. All these correlations were significant for 95 % confidence because $p \leq 0.05$. The rest of the variables were not linearly correlated (Table 4).

Eta correlation coefficient

Values of η revealed that the gender had good association with H and R/H^2; moderate association with R/H and Xc/H^2. In addition, d-ECOG-fs had moderate association with R/H and R/H^2. The rest of variables had minimum and low associations (Table 5).

Principal Components Analysis

Although graphics of outliers were not shown, it was revealed the non-existence of outliers (all points were below the default reference line (5.568 fixed in the Minitab® 14 statistical program) when the pair (R, Xc), (R/H, Xc/H) or (R/H^2, Xc/H^2) was included in PAC. Furthermore, eigenvalues, eigenvectors, proportion and cumulative proportion and variable weights by each one of PCs were shown for pairs (R, Xc) (Table 6); (R/H, Xc/H) (Table 7) and (R/H^2, Xc/H^2) (Table 8). Tables 6, 7 and 8 showed that first five, four and four PCs prevailed, respectively.

The first five (Table 6) and four (Tables 7 and 8) PCs prevailed. In Table 6, variables most correlated to PC1 were H (negatively), P_o (negatively) and d-ECOG-fs (positively). Variables most correlated negatively to PC2 were Xc, R and BMI. Variables most correlated to PC3 were age (positively) and Xc (negatively). Variables most correlated to PC4 were age (negatively), θ (negatively) and R (positively). Variables most correlated to PC5 were the LCS (positively) and LCHV (negatively). Variables most correlated to PC1 were H (negatively) and the gender (positively). Variables most correlated (negatively) to PC2 were Xc/H and the BMI. Variables most correlated (positively) to PC3 were the age and the LCHV (Table 7).

Variables most correlated to PC1 were H, R/H^2 (positively) and the gender (negatively). Variables most correlated (negatively) to PC2 were the BMI, Xc/H^2 and P_o. Variables most correlated (positively) to PC3 were the age and LCHV (Table 8).

Positions of each one of independent variables and NDLCAPs in each quadrant are showed in a two-dimensional photograph of an eleven-dimensional reality (Figure 1). Influence charts (Figures 1a,c,e) and score graphics (Figures 1b,d,f) were showed for the ordered pair (R, Xc) (Figures 1a,b) (R/H, Xc/H) (Figures 1c,d) o (R/H^2, Xc/H^2) (Figures 1e,f) included in PCA.

For the ordered pair (R, Xc) included in PCA (Figure 1a), variables were located in each quadrant: Quadrant I (age), Quadrant II (H), Quadrant III (P_o, θ, Xc and BMI) and Quadrant IV (gender, R, d-ECOG-fs, LCS and LCHV). Similar distribution of these variables was observed when in PCA was included the ordered pair (R/H, Xc/H) (Figure 1c) or (R/H^2, Xc/H^2) (Figure 1e), except for Xc (changed from Quadrant III to Quadrant IV) and d-ECOG-fs (changed from Quadrant IV to Quadrant I).

Discussion

Non-small cell type, male gender, age group 60-80 years, adenocarcinoma histological variety and advanced stages (IIIB and IV) prevail in NDLCAPs confirm results reported in (1, 12). The M/F = 1.56 agrees with the current trend of increasing the number of lung cancer women (M/F tends to 1 in next years) due to changes in their lifestyle and smoking habits, aspects that may justify why adenocarcinoma has displaced squamous cell carcinoma [1].

The negative correlation between H and gender confirms that men are generally taller than women, aspect corroborated with correlations of gender with H, R/H and R/H^2; and correlations of H with R/H and R/H^2. Moderate correlation between H and P_o

corroborates that decrease/increase in P_o does not lead necessarily to decrease/increase of H. Despite good correlation between BMI and P_o, severe decrement in ΔP is better predictor than P_o and BMI for the evaluation of malnutrition, tumor activity (due to catabolism), poor prognosis, low quality of life, and short survival of LCAPs [13]. d-ECOG-fs does not depends on gender is corroborated by low correlation between them. Low and negative correlations of d-ECOG-fs with P_o and H indicate that the increase of d-ECOG-fs is not necessarily associated to decrease of P_o and H, and d-ECOG-fs is subjective (depends on patient criterion and the physician appreciation). Non lineal correlation between d-ECOG-fs and LCS may be explained by predominance of stages IIIB and IV in NDLCAPs, in agreement with [19] and in contrast with [20].

sEGF, sCYFRA 21-1 and sCA 72-4 concentrations in their respective normal ranges for most of NDLCAPs with no history of breast cancer are in contract with high concentrations reported in LCAPs [3, 21]. The large standard deviation/standard errors of the mean of three biomarkers may be due to the biological individuality among NDLCAPs and marked variability of their values (normal and increased respect to those in AHASs).

Minimum linear correlation/association between d-ECOG-fs and θ is an unexpected result because both variables are separately indicators of the deterioration of the general condition of health and unfavorable prognosis of LCAPs [1, 4-6, 13]. This may be explained because d-ECOG-fs is a subjective variable whereas θ value is quantitative, and/or d-ECOG-fs 3 and normal θ values prevail in the majority of NDLCAPs. As a result, general health of each one NDLCAPS has not been essentially affected yet by the presence of LCHV, corroborating small differences between means ± standard errors of θ_r and θ for each age group and gender.

The minimum/low correlation degree and low/moderate association degree of LCS with BBVs may be explained because stages IIIb and IV prevail in the 82.6 % of NDLCAPs (no receive any anti-cancer therapy and 13.04 % of them take only diuretics), in agreement with Toso and colleagues [4], who report that distribution of the impedance vector is the same for both stages in LCAPs.

Correlation of gender and H with R/H and R/H^2, and high degrees of correlation and association of R/H^2 with d-ECOG-fs corroborate that R/H^2 may offer information more approximated, respect to R and R/H, of body electrical conductor volume of NDLCAPs. Distributions of R/H values contradict that R/H does not change in LCAPs with stages IIIb and IV [4], and agree with findings of Nwosu and colleagues [6]. Furthermore, the non-prevalence of highest R/H values, respect to its normal range, verifies the non-dehydration observed clinically in NDLCAPs, in contrast with Cerchietti and colleagues [22]. These findings confirm that dehydration/overhydration of any individual is closely related to the increase/decrease of R, R/H and R/H^2 [4-7]. Patients with Codes 10 and 16 should be dehydrated by high R/H values, in contrast with clinical observations, and explained from their cachexia and severe decrease in ΔP (decrease of waist/hip ratio) and therefore decrease of body electrical conductor area/volume. The decrease/increase of R/H values in NDLCAPs may be also due to the retention/release of a high water amount by the inadequate/activation secretion of their antidiuretic hormones. Increase of sEGF, sCYFRA 21-1 and sCA72-4 concentrations, and decrease of R/H are only observed in one patient (Code 21); therefore, we discard the retention of total body water due to the increase in hormonal activity (associated with the lung cancer growth) [19]. Hormonal processes are decreased in elderly patients [23]. These aspects may explain why R/H and $(R/H)_r$ average values in female patients for the 17 to 59 and 60 to 80 age groups differ. Additionally, higher mean of R/H and $(R/H)_r$ values in the 60 to

80 age group compared to those in their respective 17-59 age groups may be explained because elderly individuals (NDLCAPs and AHASs) have decrease their total body fluids due to the decrease in osmolority, number of nephrons, percentages of glomeruli and the ability of the kidney to concentrate urine by the increase vasopressin secretion, among others [23]. That is why, R/H average values of NDLCAPs of the 60 to 80 age groups are similar for both genders.

Variability in PBVs, TBVs and BBVs explain why we recommend the individual integrated analysis of each one of them respect to its normal range, instead of comparison of their means between NDLCAPs and AHASs. Furthermore, TBVs and PBVs are necessary but not sufficient to evaluate integrally NDLCAPs. Therefore, we add BBVs to this integrated analysis.

Correlations between R/H and R/H^2, R/H and R, and R/H^2 and R may explain the increase/decrease of R/H in NDLCAPs from the decrease/increase of σ ($\sigma = 1/\rho = \sum_{i=1}^{m} q_i v_i n_i + \sum_{j=1}^{k} q_j v_j n_j$), where $q_{i,j}$, $v_{i,j}$ and $n_{i,j}$ ($i \neq j$) are the electric charge, velocity and concentration of the i-th positively charged carrier ($i = 1,\ldots, m$; e.g., sodium, magnesium, calcium and potassium ions; and positively charged molecules in moving) and j-th negatively charged carrier ($j = 1, ..., k$; e.g., chlorine, phosphates, bicarbonate and sulphate ions; electrons and negatively charged molecules in moving), respectively. Changes in $v_{i,j}$ and $n_{i,j}$ ($i \neq j$) of these charged carriers lead to alterations in σ and therefore the hydric state of NDLCAPs/LCAPs.

The non-linear correlation between R and Xc, and the moderate correlations of R/H with Xc/H, and R/H^2 with Xc/H^2 confirm that in graphics that show confidence regions (Xc versus R, Xc/H versus R/H, and Xc/H^2 versus R/H^2) should appear the tolerance rectangles (50, 75 and 90 %) and not the tolerance ellipses, in agreement with Luna and

colleagues [7]. Correlations of the gender with Xc/H and Xc/H^2 confirm that overweight prevails in women NDLCAPs, in agreement with Chooi and colleagues [24]. Accumulated explained variances between 48.0 and 52.0 % (Tables 6-8) by PC1 and PC2 may be due to biological individuality of NDLCAPs (complex, open and non-linear system); amount, type and variability of original independent variables analyzed; minimum/low/moderate linear correlation and association among some of them. Despite, PC1 and PC2 are only considered in this study by the following biophysical and clinical reasons: 1) they corroborate the above discussed; 2) selection of PCs and variables that most contribute to them do not depend on the inclusion of the pair (R, Xc), (R/H, Xc/H) or (R/H^2, Xc/H^2) in PCA because PBVs, TBVs and BBVs are characteristic of each patient. 3) PC2 is selected and no PC3 because Xc, Xc/H and Xc/H^2 weights in PC2 are greater than those in PC3. Furthermore, BMI (in PC2) is better predictor than age (in PC3) for the general health evaluation and prognosis of NDLCAPs. 4) PC2 is chosen and no PC4 because BMI and Xc/H (in PC2) are better predictors than age and R/H (in PC4). 5) Intersection of the positioning projections of NDLCAPs on PC1 and PC2 is not observed in the score graphics (Figures 1b,d,f).

The general health of NDLCAPs may be represented by the ordered pair (PC1, PC2), instead of the ordered pair (R, Xc) or (R/T, Xc/T) [7], where PC1 and PC2 may be interpreted as the prognosis and body energy reserve of NDLCAPs, respectively. This prognosis may be unfavorable (PC1 positive values) or favorable (PC1 negative values). Body energy reserve accumulates (PC2 negative values) or spends (PC2 positive values). For PC1, favorable prognostic indicators for NDLCAPs occur for the male gender; LCHV that less prevail; increases in H, P_o, θ and Xc; and decreases in d-ECOG-fs, LCS, R, R/H, R/H^2, Xc/H, Xc/H^2, and age. For PC2, indicators of depletion/loss of body energy reserve of NDLCAPs happen for the female gender; the LCHV that less

prevail; increases in H and age; and decreases in θ, P_o, R, R/H, R/H^2, Xc/H, Xc/H^2, BMI, d-ECOG-fs, and LCS. This brings about that PC5 (Table 6) is not considered in this study, in addition to reasons above-mentioned.

During writing process of this paper (3 years later initiated this study), NDLCAPs that die in the short time (two first years after they are diagnosed) located in Quadrant I; those that die after 2 years after diagnosed distributed in Quadrants IV (survival of these patients will be smaller than 5 years); cured cancer patients up to now with good general condition of health concentrated in Quadrant III (tumors of these patients will reach their complete remissions in the future); and cancer patients under treatment up to now concentrated in Quadrant II (these patients will have long survivals (greater than 5 years after diagnosed) with good/acceptable general health). Furthermore, the unfavorable prognosis is corroborated in 83.3 % of NDLCAPs that are located in Quadrant I (EGC, LGT, ITR, RSF and JLR) and Quadrant IV (NHB, OSP, NLB, EGM and ECP). Two deceased patients (ODR and OGC) are located in the vicinity of PC2 between Quadrants III and IV. A patient (OMR) who is located in Quadrant II does not die from cancer but from global heart failure. These aspects may confirm adequate interpretations of PC1, PC2 and each quadrant. As a result, NDLCAPs place in Quadrants I and IV at the moment of their diagnosis is very probable that evolve towards to the death in a short relatively time. If this hypothesis is confirmed, PCA may be a useful tool in oncology for the integral evaluation and prognosis of NDLCAPs when they receive their respective anti-cancer therapies. For this, a further longitudinal study will be required.

From bioelectrical point of view, low Xc/H values in the majority of NDLCAPs is explained by Luna and colleagues [7] from increase of cell membrane electric capacity, C_m ($Xc = 1/(2\pi f C_m$, f = 50 kHz), due to the increase of the amount of electrical charge

on both sides of the cell membrane (Q); the relative electrical permittivity (ε_r)/electrical susceptibility (χ_e) of cell membrane lipid; and decrease of the transmembrane potential of the cancer cell (V_m). For this, the equivalent electrical model of the cell membrane is the parallel flat plate capacitor ($C_m = Q/V_m = \varepsilon_r\varepsilon_o A/d = (1-\chi_e)\ \varepsilon_o A/d$), where ε_o is the electrical permittivity of the vacuum; A and d are the area and the thickness of the cellular membrane, respectively. Decrease of V_m have been associated with neoplastic transformation, cell division, depolarization of the cancer cell, weak electric coupling among cancer cells, failure of the contact inhibition mechanism, depletion of adenosine triphosphate and failure of the sodium/potassium pump, interior-exterior ionic imbalance of the cancer cell, body water imbalance and its three compartments in the cancer patient differences in cancer electrical properties respect to hose of normal tissue, among other disorders [7, 25, 26].

χ_e/ε_r may be increased by temperature (discarded because NDLCAPs and room temperatures keep constants); contaminations (for example, toxic compounds and waste products generated by the tumor), fat perforation by peroxidation lipid (probably caused by reactive oxygen species and free radicals); and own defects of cellular aging (BBVs are altered in AHASs and NDLCAPs of the 60 to 80 age group respect to those of the 17 to 59 age group. The increase of χ_e/ε_r supposes that Q displaces and accumulates, leading to the induction of an electric field cellular membrane that opposes to the physiological electric field existent at the cellular membrane (minus gradient of V_m ($-\nabla V_m$)). Furthermore, the increase of χ_e/ε_r may indicate changes in the composition, mobility, and electrical and mechanical properties of lipids in cancer cell membranes, aspect that may be related to the dyslipidemia in the majority of NDLCAPs.

Dyslipidemia has been associated with the growth, aggressiveness and metastasis in LCAPs [27] and in children with different types of cancer [7].

From thermodynamic point of view, low Xc/H values may be due to losses of body energy reserves that may lead to the tiredness and the fatigue that NDLCAPs refer, being remarkable for the 60 to 80 age group (negative correlation between Xc and age), in agreement with [4, 5, 7]. This may explain why d-ECOG-fs is not linearly correlated and minimally associated with Xc, Xc/H and Xc/H^2 and not only from several patients have their Xc/H values in the normal range. NDLCAPs with marked depletion of body energy reserves may explain nutritional status deterioration in them (cachexia, and/or decreases in P_o, ΔP and BMI documented in some NDLCAPs). Consequently, inadequate general conditions of health of them (corroborated by prevalence of d-ECOG-fs 3 and 4). These energetic losses may occur when the amount of heat transmitted to the environment through human body parts increases by the increase in the total dissipation of losses ($P_{dissipated}$). This $P_{dissipated}$ originates in the organism by the increase of its associated dissipation factor, which increases when the equivalent electrical resistance and the equivalent electrical capacity at body level increase too, since the harmonic frequency remains constant (50 kHz).

The complete depletion of NDLCAPs body energy reserve would occur for the highest value of $P_{dissipated}$ (heat completely transmitted to the environment) and therefore they would die, in contrast with the fact that NDLCAPs are alive at the time of their diagnosis. To avoid this, transmitted heat is limited by the induction of a thermal resistance (R_T) in the organism that is responsible of temperature difference between the body and the environment (ΔT, $\Delta T = P_{dissipated} R_T$).

As the body temperature of each patient and the environmental temperature remain constants during the measurements, ΔT may be considered constant, which supposes that $P_{dissipated}$ decreases by a certain proportion and R_T increases by the same proportion (verified because R/H mean value is higher than $(R/H)_r$. Decrease in $P_{dissipated}$ is a

measure of the increase in body entropy variation because R and R_T increase and it may be compensated making more capacitive the human body (increase of electrical capacity at the cellular/tissue/body level) that leads to a decrease of Xc, Xc/H and Xc/H^2 in NDLCAPs. Consequently, R and Xc may be interpreted as body energy losses and reserves. An energy imbalance of Xc/R ratio may lead to an unfavorable prognosis of NDLCAPs. By contrast, an energy balance between Xc and R may explain why most of θ values are in their normal range for NDLCAPs. These findings agree with Luna and colleagues [7].

The prevalence of minimal, low and moderate degrees of linear correlation/association among PBVs, TBVs and BBVs may be due to variables of the psycho-neuro-endocrine-immune system (NDLCAPs are bio-psychosocial beings [28]) are not considered. Another reason may be that dependent and independent variables are indirectly related by different ways. Firstly, the dependent variable is a function of one variable that in turn depends on another and so on until the last variable is related to the independent variable. Secondly, the dependent variable depends on multiple independent variables that interact among them. Thirdly, the relationship between dependent and independent variables is affected by the influence of confusing (influence on both independent and dependent variables), intervening (affect the dependent variable but cannot be measured or manipulated) and/or moderating (alter the effect that an independent variable has on the dependent variable) variables. Consequently, all these variables are necessary but not sufficient conditions (whenever the cause is produced do not implicate that always cause change in the effect). Therefore, it becomes difficult to interpret NDLCAPs biophysical states (non-linear and open systems) and establish a cause-effect relationships and possible prognosis of them. This may be explained because none of these variables are state variables (i.e., temperature, pressure, volume, entropy, Gibbs

free energy, Helmholtz free energy, enthalpy, chemical potential) that describe the state of a dynamical system (open or not) [7, 29-31]. These state variables may be related with heat and work that make the human body in presence of a cancer type. For instance, changes in patient volume is a measure of losses of unintentional body weight the patient and cachexia; variations of patient entropy, Gibbs free energy, Helmholtz free energy, enthalpy, chemical potential, heat and work are a measure of body disorder induced by the cancer in it. Therefore these thermodynamic variables should be included in this integrated analysis for the characterization and possible prognostic of NDLCAPs.

Conclusions

In conclusion, the clinical, bioelectrical and functional variables allow the integrated analysis and possible prognostic of NDLCAPs. The decrease of Xc is the most influence to losses of body energy reserve that lead to alteration of the overall health, tiredness and decreases of the weight and body mass index of these patients.

List of abbreviations

LCAPs, lung cancer adult patients; sEGF, Epidermal Growth Factor; sCYFRA21-1, fragment of cytokeratin 19; sCA 72- 4, glycoprotein TAG-72; ECOG, Eastern Cooperative Oncology Group; H, height of the subject; AHASs, apparently healthy adult subjects; BBVs, bioelectrical variables; R, electrical resistance; Xc, capacitive electrical reactance; $|Z|$, electrical impedance modulus; θ, phase angle; R/H, electrical resistance/height of the subject; Xc/H, capacitive electrical reactance/height of the subject; H^2/R, electrical resistance/(height of the subject)^2; H^2/Xc, (capacitive electrical reactance/height of the subject)^2; $(R/H)_r$, normal range of R/H; $(Xc/H)_r$, normal range of

Xc/H; θ_r, normal range of θ; PCA, Principal Component Analysis; PBVs, patient biological variables; TBVs, tumor biological variables; NDLCAPs, newly diagnosed lung cancer adult patients; BMI, body mass index; d-ECOG-fs, degree of the ECOG-fs; LCS, lung cancer stage; LCHV, lung cancer histological variety; M, male gender; F, female gender; TNM, Tumor, nodule and metastasis; ΔP, unintentional body weight of each NDLCAPs; P_e, expected patient weight if he did not have cancer; P_o, measured body weight; Ag/AgCl, Silver/Silver Chloride; N, total number of patients.

Declarations

Ethics approval and consent to participate

This study is approved at the hospital General Santiago "Dr. Juan Bruno Zayas Alfonso", Santiago de Cuba, Cuba. The final protocol was approved by the Ethics committee (Current Controlled trials BIACANCER108823SC900-149; May 5, 2017) and Scientific Board (Resolution 189/2017; June 7, 2017) of the hospital Infantil Sur Antonio María Béguez César, Santiago de Cuba. Name of the register of this Pilot study is BIACANCER and its registration data is July 6, 2017 at the Universidad de Ciencias Médicas, Santiago de Cuba, Cuba. Date of enrolment of the first participant in this Pilot study is September 4, 2017. Written Informed Consent is obtained from each participant before entering the trial.

Consent for publication

Not applicable

Availability of data and materials

All datasets generated or analyzed during the current study appear explicitly in Tables.

Competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships. We declare no competing interests.

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Authors´ contributions

Study concepts: JCCR, SCAB, LEBC. Study design: JCCR, SCAB, MMG, LEBC. Data acquisition: JCCR, TTBL, SCAB, MPR, BLR, APF, JLGB, JCNG, ECF. Quality control of data and algorithms: JCCR, MPR, LZM, MMG, LEBC. Data analysis and interpretation: JCCR, TTBL, SCAB, MPR, LZM, BLR, APF, JLGB, AMP, MMG, JCNG, ECF, LEBC. Statistical analysis: JCCR, LZM, LEBC. Manuscript preparation: JCCR, SCAB, LZM, MMG, LEBC. Manuscript editing: JCCR, LEBC. Manuscript review: JCCR, TTBL, SCAB, MPR, LZM, BLR, APF, JLGB, AMP, MMG, JCNG,

ECF, LEBC. LEBC reviewed the final manuscript. All authors contributed to multiple revisions and approved the final manuscript. An outline of the manuscript was established during five meetings, at which the authors collectively drafted and ranked the discussion topics and challenges.

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Figures

Fig.1. Projections of the observations in the component plane (graph of the second principal component against the first principal component). (a) Influence graphic for R and Xc. (b) Score graphic for R and Xc. (c) Influence graphic for R/H and Xc/H. (d) Score graphic for R/H and Xc/H. (e) Influence graphic for R/H^2 and Xc/H^2. (f) Score

graphic for R/H^2 and Xc/H^2. The variables in the influence graphs (Figures 1a, c, e) represented age (X_1), gender (X_2), patient weight (X_3), H (X_4), θ (X_7), degree of ECOG functional scale (X_8), tumor stage (X_9), tumor histological variety (X_{10}), BMI (X_{11}). The variable X_5 symbolized R (Figure 1a), R/H (Figure 1c) and R/H^2 (Figure 1e). The variable X_6 denoted Xc (Figure 1a), Xc/H (Figure 1c) and Xc/H^2 (Figure 1e). In the score graphics were represented the name initial of each patient corresponding to its code showed in Table 1: Code 1 (NPB), Code 2 (OMR), Code 3 (NHB), Code 4 (RSF), Code 5 (LGT), Code 6 (HMR), Code 7 (MBZ), Code 8 (ODR), Code 9 (OGC), Code 10 (JIRB), Code 11 (EGM), Code 12 (EPI), Code 13 (ITR), Code 14 (JRL), Code 15 (VTT), Code 16 (JCRO), Code 17 (RMP), Code 18 (ECP), Code 19 (EGC), Code 20 (NLB), Code 21 (OSP), Code 22 (CPI) and Code 23 (RGF). Patients with initials NHB, OSP, NLB, EGM, ECP, EGC, LGT, ITR, RSF, JLR, ODR, OGC and OMR deceased during the writing of this paper (Figures 1b, d, f). The patient OMR died by global heart failure.

Tables

Table 1 Characteristic variables in each newly diagnosed lung cancer adult patient

Table 2 Mean ± standard error of the mean of sEGF, CYFRA21-1, and CA 72-4 tumor marker values for apparently healthy subjects and newly diagnosed lung cancer adult patient

Table 3 Mean ± standard deviation (standard error of the mean) of R/H, Xc/H and θ (newly diagnosed lung cancer adult patients) and $(R/H)_r$, $(Xc/H)_r$ and θ_r (apparently healthy subjects), by age group and gender

Table 4 Spearman's rho correlation r (probability p) for each pair of variables analyzed

Table 5 Eta correlation coefficients

Table 6 Eigenvalues and eigenvectors of the correlation matrix of 11 independent variables considering R and Xc

Table 7 Eigenvalues and eigenvectors of the correlation matrix of 11 independent variables considering R/H and Xc/H

Table 8 Eigenvalues and eigenvectors of the correlation matrix of 11 independent variables considering R/H^2 and Xc/H^2

Figures

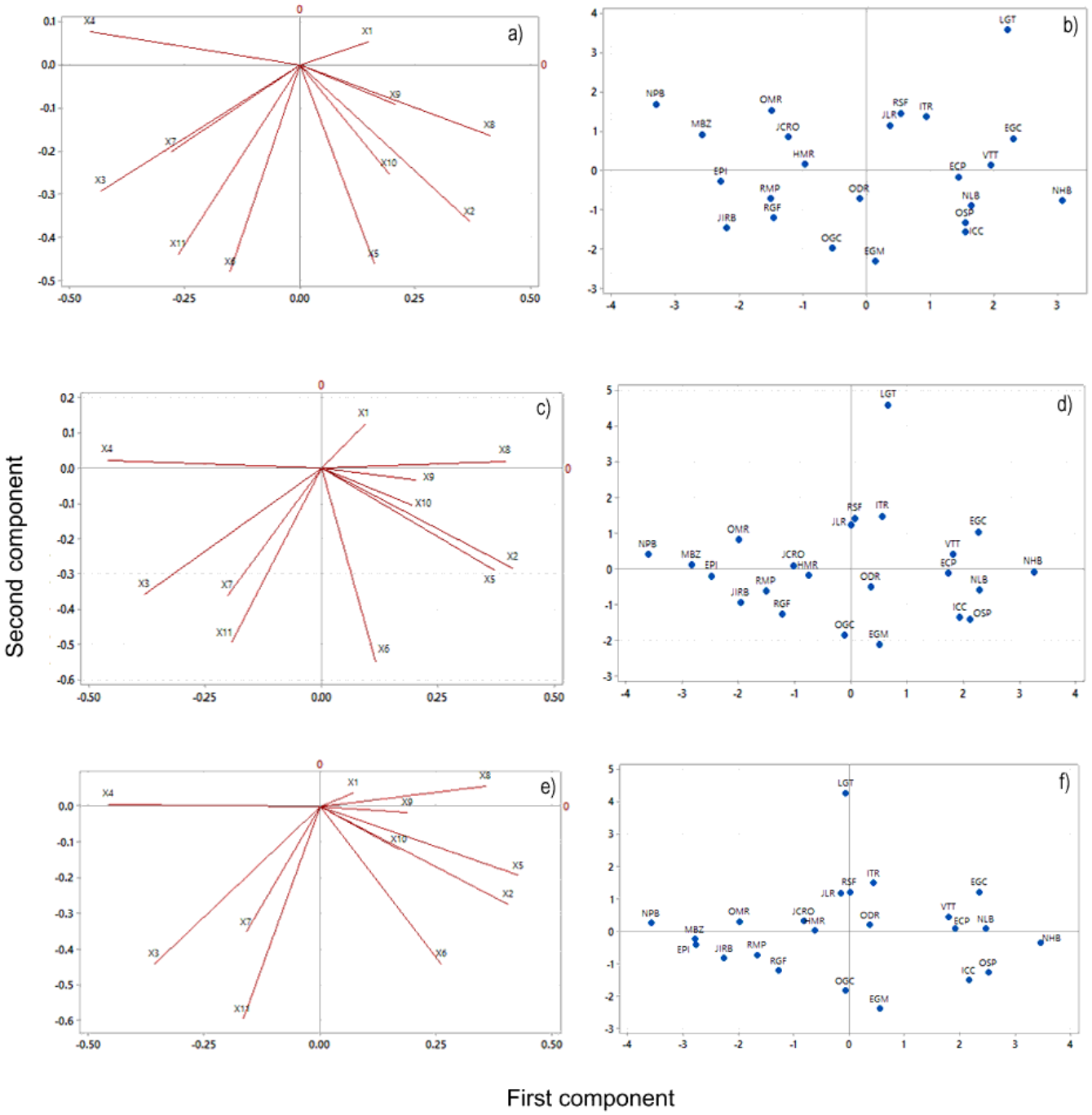

Figure 1

Projections of the observations in the component plane (graph of the second principal component against the first principal component). (a) Influence graphic for R and Xc. (b) Score graphic for R and Xc. (c) Influence graphic for R/H and Xc/H. (d) Score graphic for R/H and Xc/H. (e) Influence graphic for R/H^2

and Xc/H^2. (f) Score graphic for R/H^2 and Xc/H^2. The variables in the influence graphs (Figures 1a, c, e) represented age (X_1), gender (X_2), patient weight (X_3), H (X_4), q (X_7), degree of ECOG functional scale (X_8), tumor stage (X_9), tumor histological variety (X_{10}), BMI (X_{11}). The variable X_5 symbolized R (Figure 1a), R/H (Figure 1c) and R/H^2 (Figure 1e). The variable X_6 denoted Xc (Figure 1a), Xc/H (Figure 1c) and Xc/H^2 (Figure 1e). In the score graphics were represented the name initial of each patient corresponding to its code showed in Table 1: Code 1 (NPB), Code 2 (OMR), Code 3 (NHB), Code 4 (RSF), Code 5 (LGT), Code 6 (HMR), Code 7 (MBZ), Code 8 (ODR), Code 9 (OGC), Code 10 (JIRB), Code 11 (EGM), Code 12 (EPI), Code 13 (ITR), Code 14 (JRL), Code 15 (VTT), Code 16 (JCRO), Code 17 (RMP), Code 18 (ECP), Code 19 (EGC), Code 20 (NLB), Code 21 (OSP), Code 22 (CPI) and Code 23 (RGF). Patients with initials NHB, OSP, NLB, EGM, ECP, EGC, LGT, ITR, RSF, JLR, ODR, OGC and OMR deceased during the writing of this paper (Figures 1b, d, f). The patient OMR died by global heart failure.