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Correlations between health indicators in women who survived breast cancer

Correlações entre indicadores de saúde em mulheres que sobreviveram ao câncer de mama

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The increase in breast cancer survivors (BCS) has established unprecedented demands on health systems worldwide. In this context, new knowledge is needed to subsidize strategies to handle this population. The objective of this study was to combine the correlations between anthropometric, hematological, biochemical, biophysicochemical, muscle strength, and age variables in BCS. Twenty-two volunteers (51.7 ± 9.2 years old) with a history of mastectomy and lymphadenectomy participated in the study. Among the results, the correlations of the body mass index with lipid profile, strength, and body composition draw special attention. The associations of lipid profile with erythrocyte membrane stability, body composition, and leukocyte count, the associations of the red cell distribution width (RDW) with body mass index, lipid profile, and strength, and the positive correlation between age and leukocyte count also deserve highlights. Such findings allow concluding that investigations that deal singly with health indicators represent a severe limitation in the study of the public in question, and it is necessary to avoid them. The complex network of interactions observed between the various parameters studied reinforces the importance of a global biological analysis of attractive cost-benefit and great practical potential. Teams with medical, nutrition, physical therapy, and physical education professionals, among other areas, can use this knowledge to improve BCS's interdisciplinary approaches in short, medium, and long-term management.
Keywords: breast neoplasms, health status indicators, health promotion.

O aumento no número de sobreviventes de câncer de mama (SCM) tem estabelecido demandas notáveis sobre os sistemas de saúde em todo o mundo. Nesse contexto, novos conhecimentos são necessários para subsidiar estratégias voltadas ao manejo desse público. O objetivo desse trabalho foi analisar de modo combinado as correlações entre aspectos antropométricos, hematológicos, bioquímicos, biofisicoquímicos, de força muscular e idade em mulheres SCM. Vinte e duas voluntárias (51.7 ± 9.2 anos de idade) com histórico de mastectomia e linfadenectomia participaram do estudo. Dentre os resultados, chamam especial atenção as correlações do índice de massa corporal com perfil lipídico, força e composição corporal. As associações de perfil lipídico com estabilidade da membrana eritrocitária, composição corporal e contagem de leucócitos, as associações de RDW (*red-cell distribution width*) com índice de massa corporal, perfil lipídico e força, e a correlação positiva entre idade e leucócitos também merecem destaques. Tais achados permitem concluir que investigações que tratam os indicadores de saúde de maneira isolada representam séria limitação no estudo do público em questão, sendo necessário, portanto, evitá-las. A complexa rede de interações observada entre os diversos parâmetros estudados, reforça a importância de uma análise biológica global de atraente custo-benefício e de grande potencial prático. Equipes com profissionais de medicina, nutrição, fisioterapia, educação física, dentre outras áreas, podem valer-se desse conhecimento a fim de aperfeiçoar abordagens interdisciplinares voltadas ao acompanhamento de SCM em curto, médio e longo prazo.
Palavras-chave: neoplasias da mama, indicadores básicos de saúde, promoção da saúde.

1. INTRODUCTION

The high incidence of breast cancer (BC) in countries with different socioeconomic levels is a public health problem on a world scale. In addition to the worrying data seen over the last few decades, female BC has recently reached the top list as the most common type of cancer [1]. By

2020, 2.3 million new cases were estimated, representing one in four diagnoses among women [1].

Given this scenario, consistent efforts have been employed in the fight against the disease, reverberating more breast cancer survivors (BCS) [2]. This expressive epidemiological change consolidates morbidity as a dominant factor and significantly impacts the health systems [3].

In the history of BCS, either by the disease itself or by the treatments performed, changes in anthropometry [4, 5], fatigue level [6], muscular strength [7], hematologic variables [8], lipid profile [9, 10], and cell membrane properties [11, 12], among others, are common findings. These changes are not limited to an isolated category as they reach various health indicators.

The association between increased body mass index (BMI) and the highest risk of developing a second cancer (of different types, including a BC recurrence) was recently demonstrated in BCS women [13]. Compared to women without a history of the disease, BCS also has a greater chance of developing metabolic syndrome [14] and a higher risk of death from cardiovascular disease [15]. However, despite the complexity of the human organism and wide margin for new findings in studies involving women who survived breast cancer, the number of studies involving multidimensional observations is still limited.

As the network of interactions between these factors can trigger short, medium and long-term implications on health and quality of life, a systemic and articulated analysis of health indicators emerges as a need for the first order. Thus, the objective of this study was to combine the correlations between anthropometric, hematological, biochemical, biophysicochemical, muscle strength, and age variables in BCS. This holistic approach should generate advances in the theoretical and practical fields, favoring the development of more sensitive and effective actions by professionals from different areas of health (medicine, physiotherapy, nutrition, physical education, among others) that monitor and manage this public.

2. MATERIAL AND METHODS

2.1 Participants and Experimental Design

This research was released locally through television, radio, and social networks. Twenty-two BCS (51.7 ± 9.2 years old) were recruited and formed a convenience sample, respecting the following inclusion criteria: female; history of breast surgery and lymphadenectomy; conclusion of chemotherapy or radiotherapy for a minimum of six months and a maximum of five years; absence of smoking; and abstention of alcoholic beverages. The exclusion criteria were as follows: presenting BC recurrence since the first diagnosis; residing outside the municipality where the study was conducted; not having registration and monitoring by the *Hospital de Clínicas* (HC) of the *Universidade Federal de Uberlândia* (UFU), and do not fully meet the inclusion criteria.

This observational study followed the guidelines of Resolution 466/2012 of the *Conselho Nacional de Saúde* and the principles of the Declaration of Helsinki [16]. The project was approved by the *Comitê de Ética em Pesquisas com Seres Humanos* of the UFU and registered under CAAE number 57837416.5.0000.5152/2016. All volunteers were informed about the procedures and risks associated with the study and signed a free and informed consent form.

The study was carried out from July 2017 to June 2018. For each volunteer, the measures and evaluations were conducted at two distinct moments within a 14-week interval. The correlation matrix was built based on this grouped data set (n = 44). The pre-existing link between volunteers and HC-UFU was kept during and after the study. Thus, the volunteers continued to receive medium- and long-term follow-up by the hospital's medical staff.

2.2 Anthropometry

To determine anthropometric aspects, volunteers were barefoot, wearing light clothes, and fasting for 12 hours. Body mass (kg) and height (m) were measured on a stadiometer scale

(Filizola, Sao Paulo, SP, Brazil), and the results were used to calculate BMI (kg/m^2). The body fat percentage (BFP) and the lean mass percentage (LMP) were measured by quadrupolar bioimpedance (Biospace Corp., Inbody230, Seoul, Korea).

2.3 Hematologic and biochemical parameters

Blood samples were collected after 12-hour fasting and the absence of moderate or vigorous physical activity. On the contralateral side of breast surgery, experienced professionals collected venipuncture peripheral blood samples directly in vacuum vials (Becton Dickinson, Vacutainer, New Jersey, USA) containing K3EDTA for hematological assays and in vials without anticoagulant for biochemical tests.

Hematological variables [17] – hemoglobin levels (11.5-16.4 g/dL), erythrocyte (3.9-5.6 million/mm^3), platelet (150,000-450,000/mm^3), and leukocyte counts (4,000-10,000/mm^3); values of hematocrit (Ht) (36-47%), mean corpuscular volume (MCV) (76-96 fL), mean corpuscular hemoglobin (MCH) (27-32 pg), mean corpuscular hemoglobin concentration (MCHC) (32-36 g/dL), and red-cell distribution width (RDW) (11-15%) – were determined using an automatic analyzer (Abbott Diagnostics, Abbot Park, Illinois, USA).

Biochemical variables [17] – blood levels of total cholesterol (t-C) (<200 mg/dL), high-density lipoprotein cholesterol (HDL-C) (>60 mg/dL), low-density lipoprotein cholesterol (LDL-C) (<100 mg/dL), very-density lipoprotein cholesterol (VLDL-C) (<40 mg/dL), and triglycerides (TGC) (50-150 mg/dL) – were determined using specific commercial kits and an automatic analyzer (Cobas 6000, Roche Diagnostics GMBH, Mannheim, Germany). t-C/HDL-C (<4.0) and LDL-C/HDL-C (<2.5) ratios were also calculated [18].

2.4 Biophysicochemical variables: osmotic stability of erythrocytes

The osmotic stability test was conducted in a duplicate series of mini tubes (Eppendorf, Hamburg, Germany), each containing 1.5 mL of NaCl at concentrations ranging from 0.1 to 0.9 g/dL. Initially, the mini tubes were incubated for 10 minutes at 37 °C in a thermostatic bath [19]. After pre-incubation, 10 µL of blood was added to each tube. After homogenization, the microtubes were incubated at 37 °C for 30 minutes. Then the mini tubes were centrifuged at 1600 x *g* for 10 minutes, and their supernatants were subjected to absorbance reading at 540 nm (A540) in a UV-Vis spectrophotometer (Hach, Model DR 5000, Düseldorf, Germany).

The A540 chart as a function of NaCl (X) concentration was adjusted by sigmoidal regression according to Boltzmman's equation:

$$A_{540} = \frac{A_{max} - A_{min}}{1 + e^{(X - H_{50})/dX}} + A_{min} \quad (1),$$

in which A_{max} and A_{min} represent, respectively, the maximum and minimum plateaus of A_{540}, H_{50} is the NaCl concentration that releases 50% of hemoglobin molecules of the erythrocyte population, and dX represents a quarter of NaCl concentration variation responsible for promoting 100% of hemolysis.

Osmotic stability analyzes were performed for all volunteers. Figure 1 has a typical curve used to determine the parameters considered in this study.

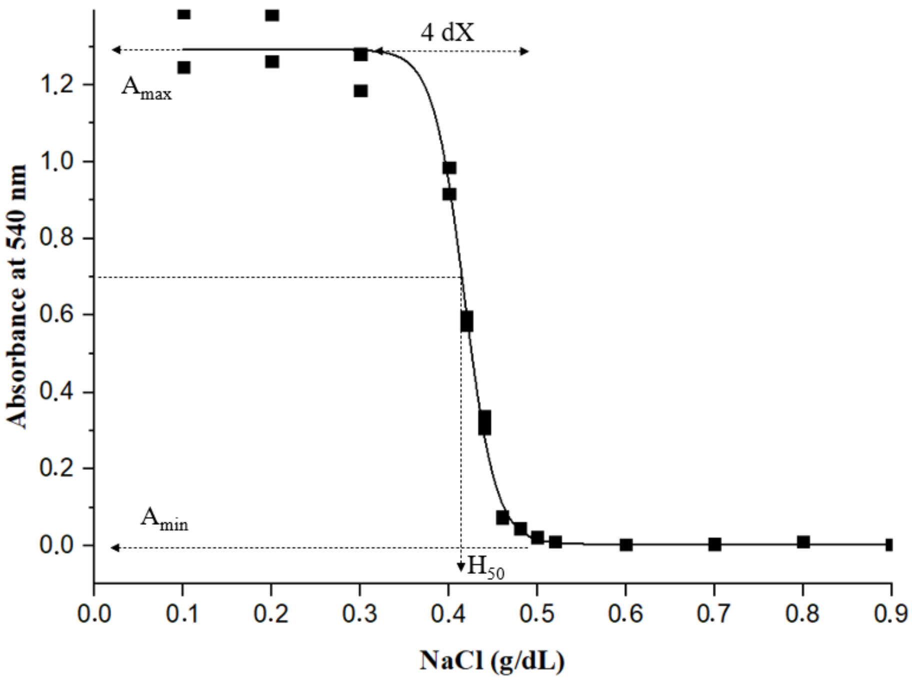

Figure 1: Typical osmotic lysis curve of erythrocytes from one of the study volunteers. Abbreviations: A_{max}: maximum absorbance plateau at 540 nm in the osmotic stability test; A_{min}: minimum absorbance plateau at 540 nm in the osmotic stability test; H_{50}: NaCl concentration that releases 50% of hemoglobin molecules from the erythrocyte population; dX: a quarter of the NaCl concentration variation responsible for promoting 100% hemolysis.

2.5 Biophysicochemical variables: mechanical stability of erythrocytes

For the determination of erythrocyte mechanical lysis kinetics, aliquots of 250 µL blood and 49.75 mL of 0.9 g/dL NaCl solution were subjected to mechanical aggression by a rotating propeller under the command of an 8000 rpm rotor for periods of 0.5; 1; 1.5; 2; 2.5; 3; 3.5; 4; 4.5; 5; 5.5; and 6 minutes [20]. After every 30 seconds of agitation, 1 mL suspension aliquots were removed, added to mini tubes (EPPENDORF, Hamburg, Germany), and then centrifuged at 1600 x *g* for 10 minutes (Hitachi Koki, Model CFR15XRII, Hitachinaka, Japan). After centrifugation, the supernatants were carefully removed with an automatic pipette and subjected to A_{540} reading in a UV-Vis spectrophotometer (Hach, Model DR 5000, Düseldorf, Germany).

The absorbance chart to A540 as a function of time was adjusted to the hyperbole given by the Michaelis-Menten equation:

$$A_{540} = \frac{A_{mmax} t}{t_{1/2} + t} \quad (2),$$

where A_{mmax} is the maximum plateau of A_{540}, representing the maximum amount of hemoglobin released in the lysis of the entire RBC population, and $t_{1/2}$ is the time interval required for the release of 50% of the total hemoglobin present in the erythrocytes sample ($A_{mmax}/2$).

Mechanical stability analyzes were performed for all volunteers. Figure 2 has a typical curve used to determine the parameters considered in this study.

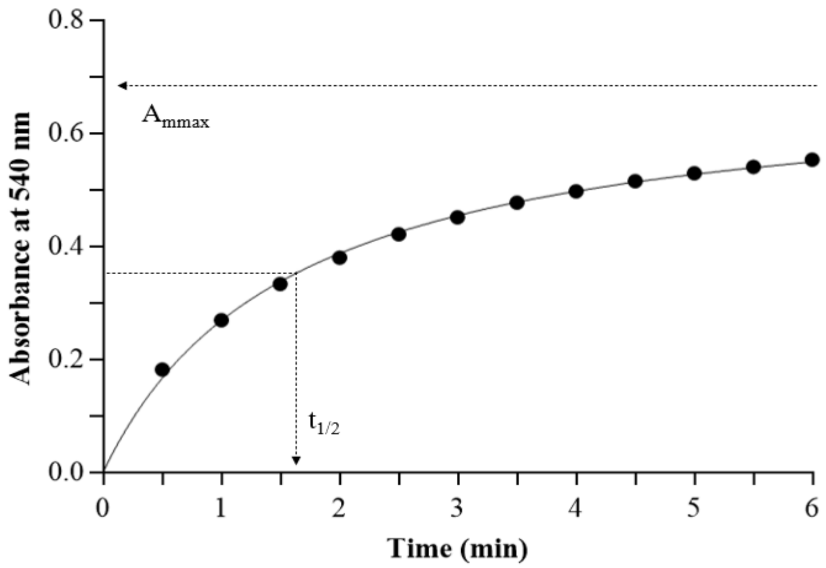

Figure 2: Typical mechanical lysis curve of erythrocytes from one of the study volunteers. Abbreviations: A_{mmax}: maximum absorbance plateau at 540 nm in the mechanical stability test of erythrocytes; $t_{1/2}$, the time interval required for the release of 50% of the total hemoglobin present in the erythrocyte sample.

2.6 Maximum strength

The determination of the maximum strength (MS) in the chest press (MSCP) and leg press (MSLP) exercises used the one-repetition maximum test (1RM). The protocol involved a specific warm-up consisting of eight repetitions with 50% of the estimated 1RM value, a two-minute interval, and another three repetitions with 70% of the estimated 1RM value. Then, five attempts were completed, with five minutes intervals between each attempt to determine the maximum load [21]. Physical education professionals supervised the volunteers and required the correct technique of execution of movements for validation of attempts.

2.7 Statistical analyzes

Data normality investigation used the Shapiro-Wilk test, and the associations between pairs of studied variables used the Spearman test. The significance level adopted was $p \leq 0.05$. GraphPad Prism 7.0 (Graphpad Software, La Jolla, CA, USA) and Origin Pro 9.0 (Microcal, Northampton, MA, USA) were used in the statistical analyses. The Corrplot Package, version 1.2.1335 (Rstudio, Boston, MA, USA), version R 3.61 (R Foundation for Statistical Computing, Vienna, Austria), was used to create the correlation matrix displayed in Figure 3.

3. RESULTS AND DISCUSSION

Growth in the number of BCS indicates the need to understand more deeply, through a holistic approach, indicators that can help monitor this population. This study is a pioneer in combining anthropometric, hematological, biochemical, biophysicochemical, muscle strength, and age analysis in BCS (Figure 3). This comprehensive view, necessary for developing a panel of analytical parameters, emerges as fundamental knowledge to achieve significant advances in the area.

The primary outcome, mainly from the correlation network with BMI and lipid profile, praises the complexity of the human organism, allowing new interpretations and actions intended for the public in question. Because they deserve special attention, these main results are discussed below. In addition, the secondary outcomes, such as those between membrane stability and hematologic parameters or between BFP and LMP, allow an even more assertive and comprehensive view of the theme.

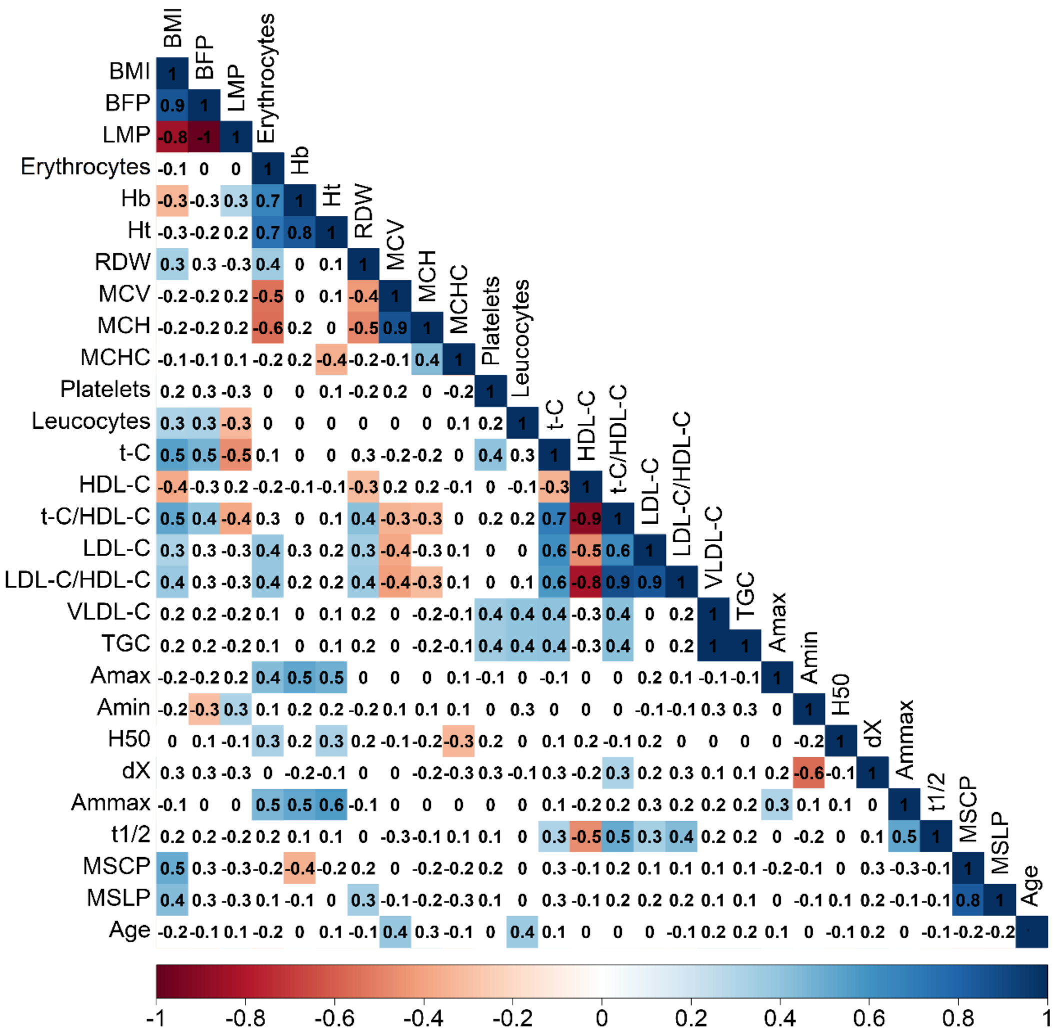

Figure 3: Correlation matrix between health indicators in women who survived breast cancer. The figure presents the Spearman rho coefficient values for the correlations between all pairs of variables. Colorful cells highlight significant results ($p \leq 0.05$), and shades of blue and red indicate positive and negative correlations, respectively. Abbreviations: BMI: body mass index; BFP: body fat percentage; LMP: lean mass percentage; Hb: hemoglobin; Ht: hematocrit; RDW: red cell distribution width; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; t-C: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; VLDL-C: very-low-density lipoprotein cholesterol; TGC: triglycerides; A_{max}: maximum absorbance plateau at 540nm in the osmotic stability test; A_{min}: minimum absorbance plateau at 540 nm in the osmotic stability test; H_{50}: NaCl concentration that releases 50% of hemoglobin molecules from the erythrocyte population; dX: a quarter of NaCl concentration variation responsible for promoting 100% hemolysis; A_{mmax}: maximum absorbance plateau at 540 nm in the mechanical stability test of erythrocytes; $t_{1/2}$: time interval required for the release of 50% of the total hemoglobin present in the erythrocyte sample; MSCP: maximum strength in chest press exercise; MSLP: maximum strength in leg press exercise.

BMI stood out for having correlations with variables of all categories analyzed, except with osmotic and mechanical stability of the erythrocyte membrane and age. These are remarkable findings for the theoretical and practical fields, as BMI is a simple, cheap, noninvasive, and widely accessible tool. Therefore, even in scenarios with limited access to equipment and exams, BMI can be adopted as a valid starting point for interpreting this integrative health panel in women who survived breast cancer.

Although BMI deals with body mass and height (kg/m^2), without providing specific data on body composition, associations observed with BFP (0.9) and LMP (-0.8) are valuable. After all, the understanding of adipose tissue as a passive energy reservoir is no longer sustained, and this tissue is already considered a crucial endocrine organ in regulating metabolism. These endocrine actions involve its ability to secrete a variety of adipokines, which participate in signaling roads that may even relate to obesity and cancer [22]. Furthermore, excessive adipose tissue accumulation tends to generate insulin resistance and diabetes [23].

An active role has also been proven for skeletal muscle in the face of its participation in glucose consumption and the (autocrine, paracrine, and endocrine) effects exerted by myokines. The various interactions these proteins mediate with other organs and tissues [24] praise the effects of the skeletal muscle on the body, including regulating immune responses [25]. Therefore, especially in physical inactivity and overweight or obesity, BMI can warn of a link between regulatory imbalances and the configuration of a pro-inflammatory environment harmful to health.

Not by chance, low-grade chronic inflammation should be a central concern along the aging process. With advancing age, in addition to changes in adipose tissue composition [26] and reduction of muscle mass [27, 28], BCS women deal with the late side effects resulting from the disease and treatment [7]. Concomitantly, these factors can establish a worrying framework of metabolic disorders and functional commitments to perform daily life activities [24].

Ahead, positive correlations between BMI and t-C (0.5), t-C/HDL-C (0.5), LDL-C (0.3), and LDL-C/HDL-C (0.4), and a negative correlation between BMI and HDL-C (- 0.4) were observed. In addition, t-C/HDL-C correlations with BFP (0.4) and LMP (-0.4) were noted. As the lipid profile has been pointed out as a risk factor for atherogenic progression and the development of cardiovascular diseases in BCS [10, 18], such findings corroborate the above reasoning and support this integrated network between anthropometric and biochemical aspects.

It is noteworthy that some authors have used the so-called obesity paradox to challenge the conception between increased adiposity and reduced survival in the cancer context. Hakimi et al. (2013) [29] indicated an association between higher BMI and lowered specific mortality for patients with renal cell carcinoma. On the other hand, Gonzalez et al. (2014) [30], working with BC patients and other cancers, showed that although this paradox was present in BMI analyses, this did not occur when obesity was defined using fat- or fat-free mass indexes. Therefore, as Lennon et al. (2016) [31] stated, the obesity paradox must be constantly confronted with the methodological picture to avoid misinterpretation.

With these counterpoints as a reference and clarity that all variables should be analyzed within their context, studying interactions between hematologic and biochemical aspects brings thought-provoking data. The directly proportional RDW relationships with LDL-C (0.3), t-C/HDL-C (0.4), LDL-C/HDL-C (0.4), and inversely proportional to HDL-C (-0.3) warn of possible impacts associated with the highest levels of cholesterol. RDW is an index reflecting erythrocyte size heterogeneity, and its increase has been associated with oxidative stress, inflammation, and, more specifically, for BCS, as a pessimistic prediction of disease-free survival and general survival [32].

Significant correlations between lipid profile and biophysicochemical aspects of erythrocyte membrane were also observed, confirming the responsiveness of erythrocytes to the microenvironment (blood) in which they are present. Concerning the variables of mechanical stability of the erythrocyte membrane, such as $t_{1/2}$, which represents the time interval required for the release of 50% of the total hemoglobin present in the erythrocyte sample, the correlations found with HDL-C (-0.5), t-C (0.3), t-C/HDL-C (0.5), LDL-C (0.3) and LDL-C/HDL-C (0.4) deserve attention. In osmotic stability analysis, the highlight goes to the association between t-C/HDL-C and dX (0.3), a variable representing a quarter of the saline variation required to promote 100% hemolysis.

Together, those data associate higher levels of total cholesterol, LDL-C, and the total and LDL-C cholesterol ratios on HDL-C with higher erythrocyte resistance to mechanical and hypotonic aggression. In addition, those data associate higher levels of HDL-C with lower mechanical and osmotic resistance of erythrocytes. These findings appear to counteract the results of the literature that associate elevation of total and LDL-C cholesterol levels with increased stiffness and decreased erythrocyte membrane deformability [33], as well as the recognized action of HDL in removing excess membrane cholesterol of extrahepatic tissues through so-called reverse cholesterol transport [34], increasing membrane fluidity [19] and erythrocyte survival [35].

There is a paradox here, whose understanding needs to consider the context of the influence of lipidemia on the composition and properties of the erythrocyte membrane. It is also noteworthy that both lack and excess fluidity can affect cell properties and lead to loss of erythrocyte stability and early destruction [19]. Up to a certain level, the erythrocyte membrane cholesterol content contributes, physiologically, to generating the so-called critical membrane fluidity. Beyond this level, higher cholesterol content contributes to decreased fluidity and rigidification of the erythrocyte membrane, with decreased deformability and erythrocyte survival. The results of this study reflect a desirable influence of greater lipidemia on the maintenance of erythrocytes, given the devastating hematological implications caused by the previous treatments of the disease. On the other hand, those findings of literature [33, 35] relate to the influence of lipidemia in populations without a history of hematological aggression.

Strength parameters also demonstrated associations with variables of different categories, generating exciting results. Positive correlations of maximum strength in chest press (MSCP) (0.5) and leg press (MSLP) (0.4) with BMI suggest that the highest ability to develop strength, both in upper and lower limbs, may be related to the highest body mass. Given the importance of muscle strength for the functional independence of the BCS [7], this would therefore be a possible benefit in situations of increased BMI. Ahead, the correlation between MSLP and RDW (0.3) is somewhat contradictory since, as stated earlier, the increase in RDW has been associated with health losses [32]. In any case, these results reinforce the interaction complexity between the various health indicators and, therefore, establish the need for frequent monitoring of this audience throughout their lives.

The correlations of leucocytes with LMP (-0.3), BFP (0.3), age (0.4), VLDL-C (0.4), and TGC (0.4) are also of high relevance because at different times (as in the diagnosis and treatment) BCS experience the action of stressors that can generate immunological deregulation [36] and increase the risk of development of comorbidities [36]. Thus, especially when placed in perspective with advancing age in BCS [37], these associations reinforce the importance of factors such as body composition [4, 5] and lipid profile [9] in the regulatory functions of metabolism and health promotion.

This study's results reveal a complex network of associations between anthropometric, hematological, biochemical, and biophysicochemical aspects with strength and age in women who survived breast cancer (Figure 4). These findings allow global biological analysis of attractive cost-benefit and great practical potential.

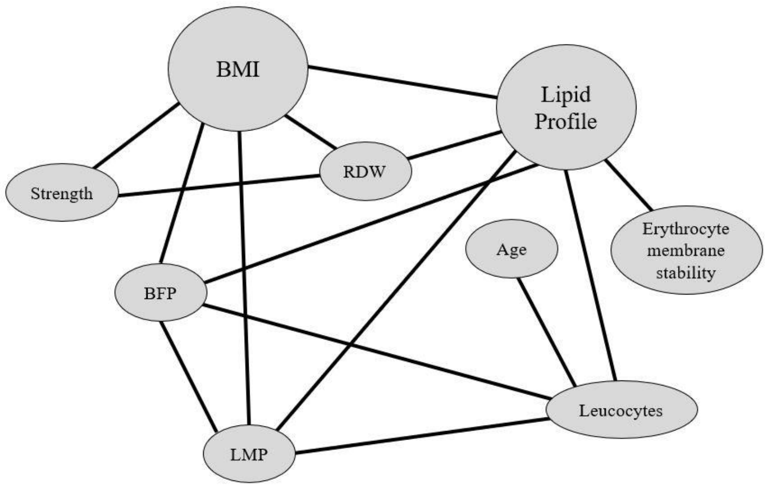

Figure 4: Network of associations between anthropometric, hematologic, biochemical, biophysicochemical, muscle strength, and age variables in women who survived breast cancer.

Abbreviations: BMI: body mass index; RDW: red-cell distribution width; BFP: body fat percentage; LMP: lean mass percentage.

This study has some limitations. Since BC's risk of recurrence remains for decades after primary diagnosis [38], the findings described here do not allow more accurate statements about long-term health indicators (e.g., five years or more). In this sense, cohort/follow-up studies should be encouraged to promote continued surveillance [7]. Another limitation is that the observed data may be context-dependent. Therefore, even if such results may alert the female population in general, it is interesting that in new studies, the samples are composed of BCS with different treatment histories (e.g., absence of breast surgery and lymphadenectomy). Despite being a problematic recruitment sample, the number of participants can also be a limitation. Finally, although the findings of this study are part of a multidimensional approach, the absence of evaluations of psychological aspects [39, 40] makes a more comprehensive understanding of the quality of life and health of BCS difficult.

4. CONCLUSION

In conclusion, BCS have a virtual network of associations between various fundamental health indicators, as noted by the BMI and lipid profile correlations with other parameters studied here. As these women are usually affected by side effects, an in-depth understanding of these indicators offers an excellent opportunity to combat morbidity and mortality in this population. Given estimates of increased breast cancer cases for the coming decades, such conduct may be a reference for theoretical-practical advances of great value. Teams with medical, nutrition, physiotherapy, physical education professionals, among others, can use this knowledge to improve interdisciplinary approaches focused on short, medium, and long-term management of women who survived breast cancer.

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