

Physical Activity's Screening in Non Metastatic Breast Cancer Patients Undergoing Surgery: An Observational Study

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Research Article

Keywords: Breast Cancer, prehabilitation, physical activity, personalized medicine

Posted Date: June 7th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-513355/v1>

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Abstract

Background

Physical activity (PA) can play a role in lowering the risk of breast cancer (BC), but also in reducing treatments related side effects, improving the quality of life and decreasing mortality in BC survivors.

Despite these benefits, the majority of BC patients do not achieve the recommended levels of PA and often reduce their exercise frequency after the diagnosis.

Moreover, PA screening and counseling are not offered to patients as standard of care, even in high quality breast units.

Methods

From February 2019 to March 2020, we performed a preoperative physical and nutritional screening in 504 consecutive BC patients waiting for surgery.

The screening included an IPAQ questionnaire to evaluate the level of physical activity, measurement of anthropometric parameters (weight, height, waist and hips circumference, BMI and Waist Hips Ratio) and evaluation of body composition using Bioelectrical Impedance Analysis (BIA).

Results

The majority of patients in our series resulted physically inactive: clustering the IPAQ scores, 47% of patients proved to be physically inactive (MET score <700), 34% moderately active (MET score 700-2520) and only 19% physically active (MET score > 2520). In addition, approximately half of the patients (49%) resulted overweight or obese, and more than half (55%) had a percentage of fatty tissue over the recommended cut off for adult women.

Conclusions

Our data confirm that assessment of PA levels should become part of the standard preoperative evaluation of BC patients and behavioral interventions should be offered to them, in order to prehabilitate to surgery and improve outcomes.

Background

An extensive number of publications and guidelines have confirmed the importance of PA both in primary and tertiary prevention of breast cancer (BC) ^{1,2,3}.

As concerns primary prevention, the International Agency for Research on Cancer (IARC) estimated a 20–40% decreased risk of BC among the most physically active women, regardless of menopausal status, type and intensity of activity ⁴.

But PA has also been shown to play a key role during and after cancer treatments: it can alleviate common side effects of oncologic therapies (such as anxiety-depression, poor sleep, lymphedema and cancer-related fatigue), increase the adherence to treatment schedules ⁵ and contribute to a significant reduction in recurrence and mortality rates ⁶.

Despite such evidence, observational studies indicate that the majority of BC patients do not achieve the recommended levels of PA and furtherly reduce them once receiving the diagnosis ^{7,8}.

In this study, we present the results of a systematic preoperative screening of PA and nutritional status in a consecutive series of non metastatic BC patients, using the IPAQ questionnaire, measurement of anthropometric parameters and body composition analysis.

Materials And Methods

From February 28, 2019 to March 6, 2020, all patients with histologically proven BC treated in the Breast Surgical Unit of the Fondazione Policlinico Gemelli underwent a preoperative physical and nutritional screening while waiting for surgery.

The screening was performed within few days from communication of diagnosis and included an IPAQ questionnaire (International Physical Activity Questionnaire) to evaluate the levels of physical activity, measurement of anthropometric parameters (weight, height, waist and hips circumference, Body Mass Index and Waist Hips Ratio) and evaluation of body composition using Bioelectrical Impedance Analysis (BIA).

All histological features were included (Table 1) and BC were divided into five different subtypes: luminal A (A), luminal B (B), luminal HER positive (BH), HER positive (H) and triple negative (TN). Patients with metastatic disease were excluded from the study because of the potential impact of systemic disease on patient's nutritional status and physical activity levels.

Ipaq Questionnaire (International Physical Activity Questionnaire)

Different types of PA performed as part of everyday life were investigated using the IPAQ questionnaire. In particular, patients were asked to report 1) all the vigorous activities performed in the last 7 days for at least 10 minutes at a time; 2) all the moderate activities performed in the last 7 days for at least 10 minutes at a time; 3) all the time spent walking in the last 7 days (at work and at home, walking from place to place and any other walking done for recreation or sport); 4) time spent sitting on weekdays during the last 7 days (at work, at home and during leisure time).

Activities that implied hard physical effort and made breathing much harder than normal were classified as "vigorous" physical activities, while activities that made breathing somewhat harder than normal were classified as "moderate".

Metabolic equivalents (METs) were used to quantify the duration and intensity of the activity combined.

METs were then converted into MET-hours per week, to define the sum of MET levels for each activity multiplied by the duration of the activity performed.

Based on a total MET-hours per week score, patients were classified as physically active (MET score > 2520), moderately active (MET score 700–2519) or inactive (MET score < 700) ^{9,10}.

Anthropometric measures

Anthropometric measures included height, weight, body mass index, waist circumference and waist-hips ratio (WHR).

Height was measured using a mechanical stadiometer (Measuring stations and column scales SECA 711; GmbH & Co. KG, Hamburg, Germany) to the nearest 0,5 cm (without shoes) in standing position, while the patient is facing directly ahead, feet together, arms by the sides, heels, buttocks and upper back in contact with the stadiometer. Weight was measured using a mechanical scale to the nearest 0.1 kg (Measuring stations and column scales SECA 711; GmbH & Co. KG, Hamburg, Germany) without clothes. Body mass index (BMI) is calculated using the following formula: kg/m². Circumferences were measured at the smallest circumference of the waist, above the belly button, at widest part of the buttocks (hip). Every measure is approximated to the nearest 0,5 cm using a stretch-resistant tape (Ergonomic circumference measuring tape; SECA 201; GmbH & Co. KG, Hamburg, Germany). Waist Hips Ratio was calculated using the following formula: Waist circumference (cm)/Hips circumference (cm).

Body composition analysis

Body composition assessment was performed using Segmental MultiFrequencies-Bioelectrical Impedance Analysis (SMF-BIA) (DS Medica model Human im touch; Milan, Italy), a safe and easy procedure routinely employed in our clinical practice. BIA consists in low electricity voltage passing through electrode patches applied on hands and feet, to measure body impedance and composition, including fat mass (FM), fat free mass (FFM) and hydration.

The exam was conducted with patients lying supine, with legs apart and arms not touching the body. All evaluations were conducted using six surface standard electrode (exa-polar) technique on the hands and feet ¹¹. Physical parameters directly measured in Ohms were resistance (Z), reactance (Xc) at 50 KHz, 800 µA phase angle (Φ) calculated using the following equation: Phase Angle = (Resistance/Reactance)* (180/π). Derived parameters considered were: Fat Mass (FM), Fat Free Mass (FFM) both in Kilograms (Kg) and percentage (%). Hydration referred to Total Body Water (TBW) was calculated in liters (L) and percentage (%).

Statistical analysis

Results from raw data were used to extrapolate main descriptive statistical parameters including mean, standard deviation and percentage for anthropometric, body composition and histopathological

information. Moreover, data from BMI, WHR and IPAQ score were used to divide the sample into different groups according to physical and nutritional status.

Statistical analysis were conducted through GRETLM software and Python scripts.

Table 1
Histopathological features. Histopathological status and BC subtypes

Histopathological status	
N° of patients	504
Grade G1 – n (%)	54 (10,52%)
Grade G2 – n (%)	258 (51,19%)
Grade G3 – n (%)	185 (36,71%)
Grade N.A – n (%)	7 (1,39%)
Estrogen Receptor positive (ER+) – n (%)	420 (83,33%)
Estrogen Receptor negative (ER-) – n (%)	81 (16,07%)
Estrogen Receptor (ER) N.A- n (%)	3 (0,60%)
Progesterone Receptor positive (PR+) – n (%)	333 (66,07%)
Progesterone Receptor negative (PR-) – n (%)	167 (33,13%)
Progesterone Receptor (PR) N.A – n (%)	4 (0,79%)
Human Epidermal Growth Factor Receptor 2 positive (HER2+) – n (%)	85 (16,87%)
Human Epidermal Growth Factor Receptor 2 negative (HER2-) – n (%)	397 (78,77%)
Human Epidermal Growth Factor Receptor 2 (HER2) N.A. n (%)	10 (1,98%)
Human Epidermal Growth Factor Receptor 2 (HER2) without FISH/SISH. n (%)	12 (2,38%)
High Ki-67 (H-Ki-67) – n (%)	285 (56,55%)
Low Ki-67 (L-Ki-67) – n (%)	191 (37,90%)
N.A Ki-67 – n (%)	28 (5,56%)
Luminal A (ER+/PR+/HER2-/ L-Ki-67) – n (%)	178 (35,32%)
Luminal B (ER+/PR+/HER2-/ H-Ki-67) – n (%)	165 (32,74%)
Luminal B (ER+/PR+/HER2+/ H-Ki-67) – n (%)	49 (9,72%)
HER2+ (ER- ; PR- ;HER2+) – n (%)	18 (3,57%)
Triple negative (ER-/PR-/HER2-) – n (%)	50 (9,92%)
In situ (DCIS)	44 (8,73%)

Results

Five hundred four (504) consecutive patients were enrolled, aged between 29 and 92 years old (mean age 57, median age 55).

Based on the results of the IPAQ questionnaire, the majority of BC patients in our cohort resulted physically inactive (47%) or only moderately active (34%) (Table 2;Fig. 1).

Almost half of the patients resulted overweight (30%) or obese (18%) (Fig. 2). Analysis of WHR [(0,88 (mean); 0,07 (SD))] and waist circumference [(91,06 (mean); 13,28 (SD))] placed patients in our cohort either in a moderate or high cardiovascular and metabolic syndrome risk group ¹¹.

Among the body composition parameters, fat mass (FM) [31,88 % (mean); 8,77 (SD)] revealed a cohort over the healthy range, while fat free mass (FFM) [68,08% (mean); 8,87 (SD)] was proven under the lower cut-off recommended (76–81%) for an adult woman (Fig. 3). Hydration (TBW [34,17 L (mean); 5,11 (SD)] [52,13% (mean); 7,13 (SD)] and phase angle [5,04° (mean);0,82 (SD)] were proven in a physiologic range in the present cohort ¹².

Table 2
IPAQ Questionnaire MET per week score

IPAQ Score	N°	%
Inactive (< 700 MET)	239	47,42 %
Moderately active (700–2519 MET)	169	33,53 %
Active (> 2520 MET)	96	19,05 %

Discussion

Physical activity (PA) is generally safe and well tolerated, even when performed during BC treatment, and has shown positive effects on cancer-related fatigue, anxiety-depression, poor sleep, lymphedema, bone health and quality of life ^{5,13,14}.

It is also associated with improved cardiorespiratory fitness, body composition as well as reduced weight gain and obesity, which are common side effects of chemotherapy and endocrine therapy in BC survivors ^{1,3}.

In addition, in the perioperative setting, PA has been shown to allow shorter hospital stay, fewer complications and faster self-assessed physical and mental recovery in more active patients undergoing breast surgery ^{15,16,17}.

PA is also associated with significant reductions in the rates of recurrence and mortality in several common cancers ¹³.

A meta-analysis of 23 prospective studies in cancer survivors documented a 24% reduction in overall mortality in patients engaging in at least 150 minutes weekly of moderate to vigorous intensity PA as compared to less physically active patients ¹⁸.

Another meta-analysis of 136 studies showed improved survival outcomes associated with higher vs lower levels of total or recreational PA for all-cancers combined (cancer specific mortality: HR = 0.82, 95% CI = 0.79 to 0.86, and HR = 0.63, 95% CI = 0.53 to 0.75, respectively) ¹⁹.

As regards BC, a meta-analysis of 16 cohort studies that included 42,602 BC patients, indicated that individuals who engaged in high levels of PA after BC diagnosis had a 29% lower risk of BC-specific mortality [RR, 0.71; 95% confidence interval (CI), 0.58–0.87; P < 0.01] and a 43% lower risk of all-cause mortality (RR, 0.57; 95% CI, 0.45–0.72; P < 0.01), compared with inactive BC survivors ²⁰.

In a recent prospective study examining different levels of activity in BC patients before diagnosis, during treatment and at 1- and 2-year intervals after enrollment, mortality was significantly reduced not only in highly-active patients (HR = 0.31, 95% CI = 0.18 to 0.53), but also in patients performing lower volumes of regular activity (HR = 0.41, 95% CI = 0.24 to 0.68), according to the Physical Activity Guidelines for Americans ²¹.

PA influences a diverse array of metabolic, hormonal and immunologic pathways, including circulating estrogen levels, insulin-like growth factors (IGFs), low-level chronic inflammation and oxidative stress, immune function, adipokines, DNA damage and telomerase activity ^{22,23}.

The Pre-Operative Health and Body (PreHAB) Study tested the impact on tissue and serum biomarkers of a pre-operative exercise intervention in 49 randomized women with newly diagnosed BC. At the end of the intervention period, there was a significant reduction in leptin (P ^{1/4} 0.008), a trend toward a decrease in IGF-1 (P ^{1/4} 0.08) and changes in tumor gene expression but not in Ki-67 measures in active participants compared with controls ²⁴.

Physically active individuals also tend to have higher sunlight exposure and consequently higher levels of vitamin D, which modulates cell proliferation ²⁵.

However, the relative influence of each pathway and their combined effects on cancer survival are still not well defined ²⁶.

Moreover, the responsiveness of specific tumor subtypes to the effects of different types and modalities of exercise is also largely unknown ^{27–34}.

Jones et al. investigated whether post-diagnosis exercise could differently affect outcomes in women with early stage BC on the basis of tumor clinicopathologic and molecular features. An exercise-associated reduction in BC-related deaths was apparent for tumors < 2 cm [HR, 0.50; 95% confidence interval (CI), 0.34–0.72], well/moderately differentiated tumors (HR, 0.63; 95% CI, 0.43–0.91), and ER

positive tumors (HR, 0.72; 95% CI, 0.53–0.97), concluding that the ER+/PR+/HER2-/low-grade clinical subtypes are those that respond better to exercise ³⁵.

In a retrospective analysis of 2,987 early BC patients, Holmes et al. found that exercise exposure (≥ 9 MET-hrs.wk) was associated with a significant 50% reduction in BC related deaths in ER positive tumors compared to a non-significant 9% reduction in ER negative tumors ³⁶.

Despite the evidence based recommendations urging cancer survivors to be physically active in order to improve acute and long term cancer-related outcomes ^{3,14,37}, the majority of cancer patients do not achieve the recommended PA levels and most of them reduce their exercise frequency after being diagnosed with BC ^{7,8}.

In our study we found 47% of the non metastatic BC patients recruited to be physically inactive and 33% only moderately active. Furthermore, almost half of the patients (49%) in our study resulted overweight or obese, 52% at high risk for metabolic syndrome, 55% with a percentage of fatty mass over the healthy range and 74 % under the lower lean mass cut off for adult women, which is consistent with a previous study of our group (submitted) ³⁸.

Data in our study confirm the importance of an adequate preoperative assessment, that should include nutritional and physical activity screening and body composition analysis in order to early detect risk factors and leverage lifestyle interventions (e.g. nutritional and psychological support, physical training, smoking and alcohol cessation) for improved treatment-related outcomes.

Since obesity and inactivity jeopardize overall health and quality of life, affordable and feasible weight management and PA services for all cancer survivors should be part of their routine cancer care.

Unfortunately, there is still a critical lack of appropriate evaluation of these parameters and a patient-centered behavioral counselling is not encompassed in the routine pathways of cancer care.

Conclusions

Despite the key role of PA in side effects management, reduction of complications and improved oncologic outcomes, little attention is devoted to this topic, even in high quality breast units.

Data that emerged from our study confirm the urgent need to include evaluation of PA and nutritional status in the routine preoperative workout of every BC patient.

In a future perspective, this comprehensive approach should require targeted exercise prescriptions, matching the biological effects of PA with cancer features, in order to convert the general advice “exercise works for everything” into a more specific prescription based on the patient’s attitudes and preferences, clinical and pathological features of the disease.

List Of Abbreviations

BC Breast Cancer

BIA Bioelectrical Impedance Analysis

BMI Body Mass Index

ER Estrogen Receptor

FFM Fat Free Mass

FM Fat Mass

HER-2 Human Epidermal growth factor Receptor 2

IARC International Agency for Research on Cancer

IGF-1 Insulin Grow Factor-1

IPAQ International Physical Activity Questionnaire

MET Metabolic equivalent of Task

N.A Not Available

PA Physical Activity

PR Progesterone Receptor

SD Standard Deviation

SMF-BIA Segmental MultiFrequencies-Bioelectrical Impedance Analysis

TBW Total Body Water

TNF Tumor Necrosis Factor

WCRF World Cancer Research Fund

WHO World Health Organization

WHR Waist Hip Ratio

Declarations

Funding: N/A

Conflicts of interest/Competing interests: The authors have no conflicts of interest to declare that are relevant to the content of this article. Author Stefano Magno declares that he has no conflict of interest. Author Maria Maddalena Rossi declares that she has no conflict of interest. Author Alessio Filippone declares that he has no conflict of interest. Author Cristina Rossi declares that she has no conflict of interest. Author Donatella Guarino declares that she has no conflict of interest. Author Claudia Maggiore declares that she has no conflict of interest. Author Annalisa Di Micco declares that she has no conflict of interest. Author Maddalena Dilucca declares that she has no conflict of interest. Author Riccardo Masetti declares that he has no conflict of interest. All authors have read and approved the manuscript. The authors declare that they have no competing interests.

Availability of data and material: Additional material are available contacting the corresponding author.

Code availability: N/A

Authors' contributions: SM (Study design, writing, review). MMR (Study design, data collection, statistical analysis, writing), AF (Data collection, writing), CR (Data collection, writing), DG (Data collection, writing), CM (Data collection), ADM (Data collection), MD (Statistical analysis), RM (writing, review)

Ethics approval: All the procedures performed during the study comply with the National and regional guidelines and European Society of Breast Cancer Specialist (EUSOMA) quality criteria updated in 2020 available at <https://www.eusoma.org/en/recommendations/breast-centre-requirements/1-148-1-> and in accordance with the ethical standards of our Institution available at <https://www.policlinicogemelli.it/scienzeinnovazione-ricerca/comitato-etico/>. Written informed consent was obtained from all participants included in the study.

Consent to participate: Informed consent was obtained from all individual participants included in the study

Consent for publication: Patients signed informed consent regarding publishing their data and photographs.

Acknowledgements

We want to acknowledge the breast nurses of our Breast Surgery Unit of Fondazione Policlinico Universitario A. Gemelli IRCCS Simona Trotta, Rosella Venturini, Maria Zagordi, Paola Del Vesco, Paola Galli, Francesca Piras, Giovanna Madeddu for their support and contribution to this study.

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Figures

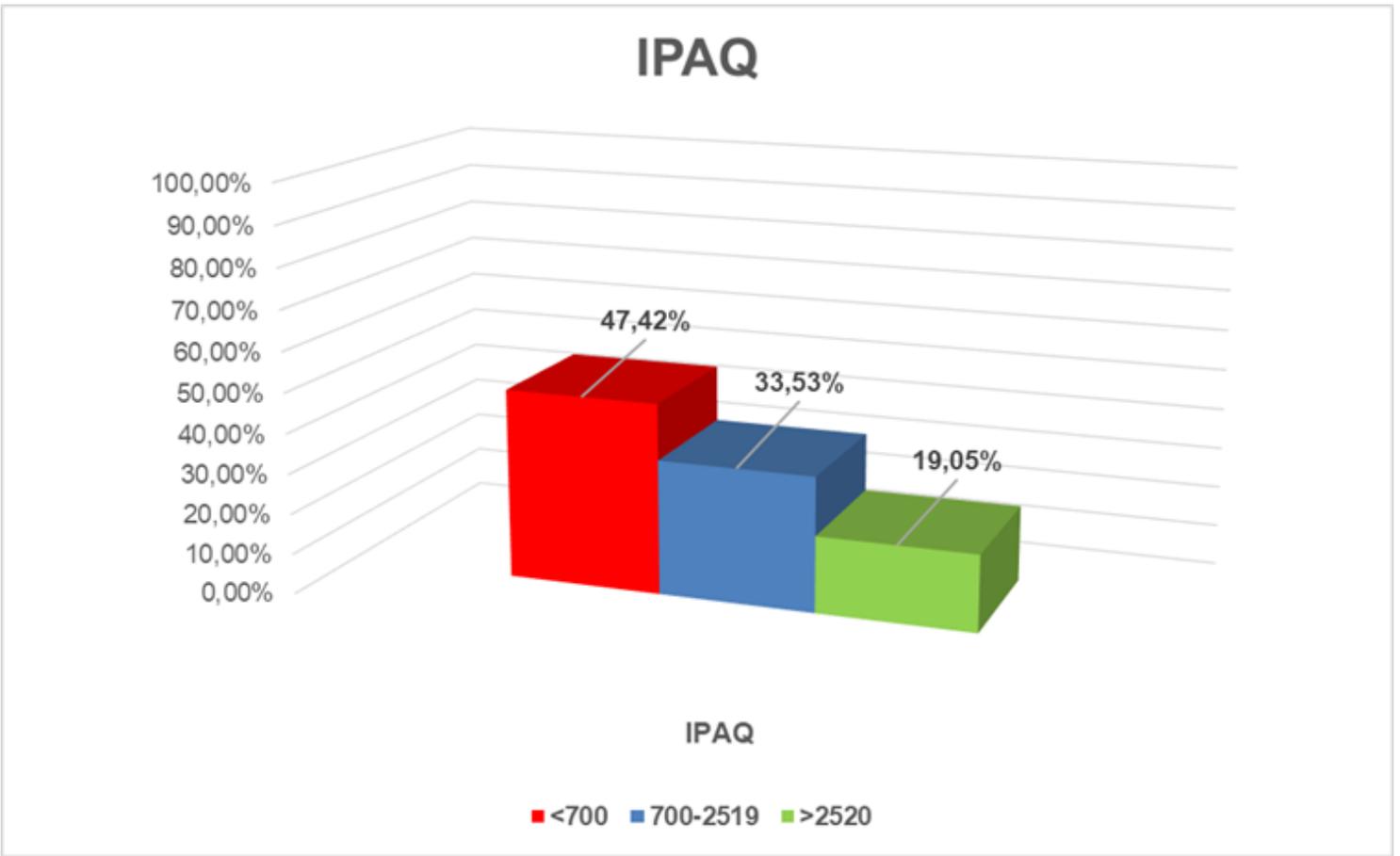


Figure 1

IPAQ Questionnaire results

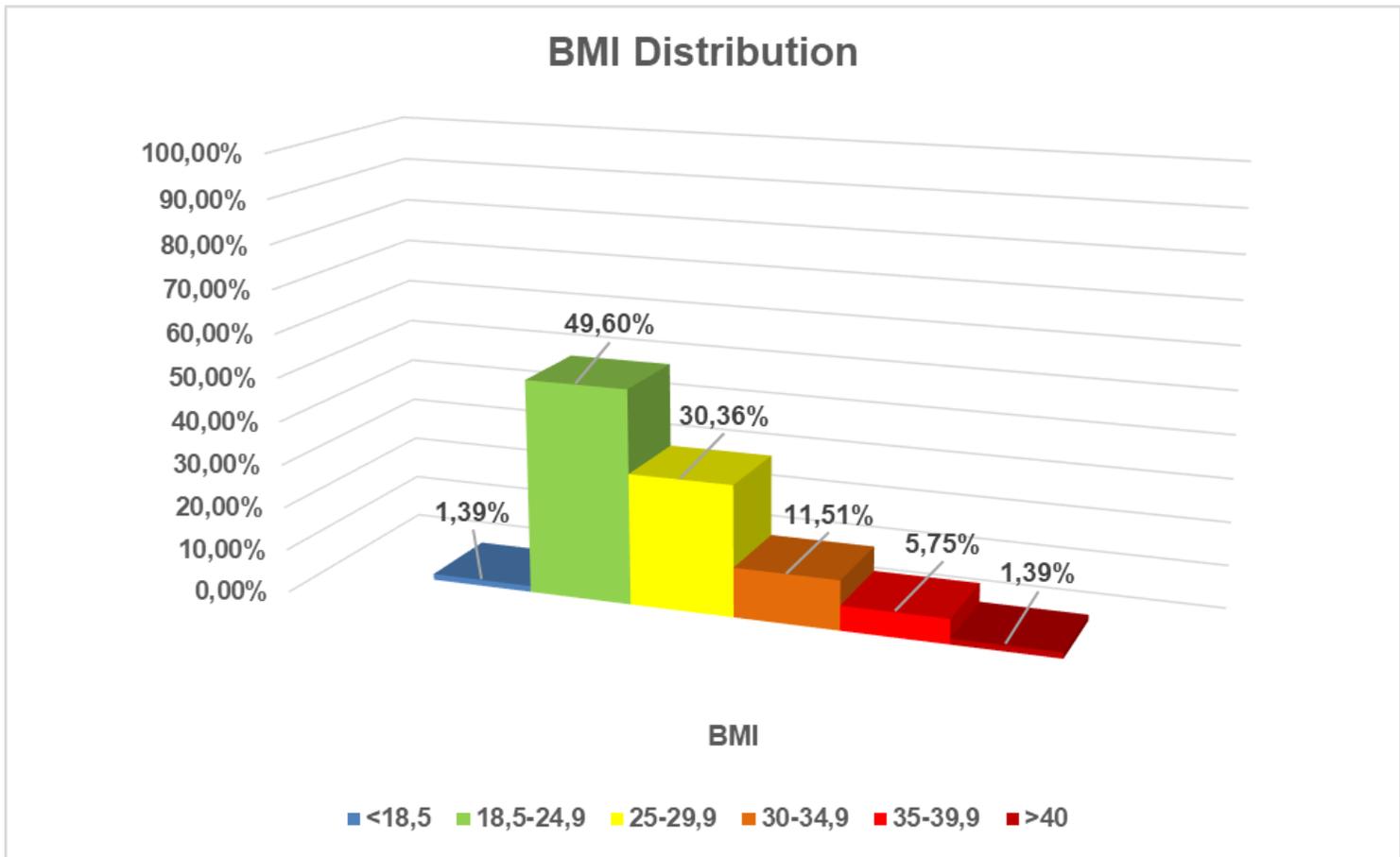


Figure 2

BMI distribution

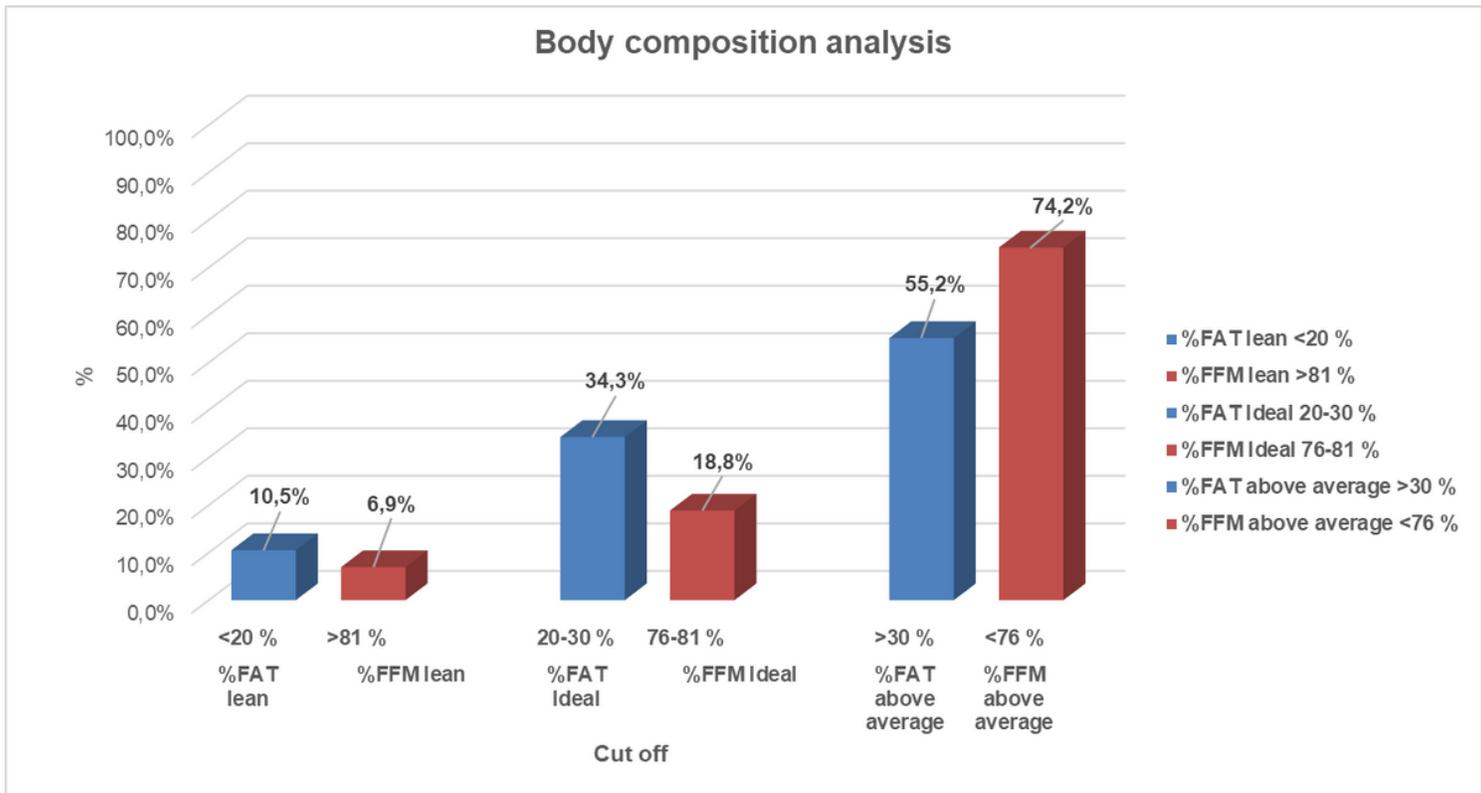


Figure 3

Body composition analysis