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Article

Exercise and Quality of Life in Patients Undergoing Active Breast Cancer Treatment: Comparison of Three Modalities of a 24-Week Exercise Program

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Simple Summary: Exercise is an accepted intervention for improving the quality of life of cancer patients, and its practice is considered safe and feasible at all stages of the oncologic process. Several studies have been conducted with different modalities of exercise programs, including traditional booklets, home-based exercise, and face-to-face sessions. However, there is a lack of research comparing these three modalities of exercise programs. This study aims to assess the effectiveness of three recommended modalities of physical exercise on quality of life in breast cancer patients actively undergoing treatment. Global quality of life improved significantly at 24 weeks in the face-to-face and home-based exercise groups, but not in the referral group, with a final sample size of 80 patients.

Abstract: Background: Exercise is an accepted intervention to improve the quality of life (QoL) of breast cancer patients. Exercise programs have been developed and all have shown satisfactory results in improving QoL. There is a lack of research comparing different prescription modalities. The aim of this study is to evaluate the effectiveness of physical exercise (in-person, home-based, prescription) on QoL in breast cancer patients actively undergoing treatment; Methods Quasi-experimental study with randomized assignment to three groups (in-person: guided and supervised in-person exercise program; home-based exercise: guided and supervised exercise program with streaming monitoring; recommendation: exercise recommendation). Quality of life was measured using the QLQ-C30 questionnaire. Baseline and 24-week analysis. Results: The total sample analyzed was n=80. QoL improved significantly at 24 weeks in the face-to-face and home-based exercise groups, but not in the advice group. Exercise in all modalities improved fatigue, nausea, vomiting, appetite, and constipation. QoL at 24 weeks depended on active chemotherapy, tumor type, and assigned exercise group ($r^2 = 0.503$; $p < 0.001$). Conclusions: QoL in breast cancer patients undergoing active treatment improves after a 24-week exercise program, especially in face-to-face and home-based exercise. Home-based exercise, streaming-based recommendation is a viable option for exercise recommendation.

Keywords: quality of life; breast cancer; chemotherapy; exercise program

1. Introduction

Breast cancer is the most common malignancy in women, accounting for 15% of all new cancer diagnoses worldwide. Its incidence is increasing due to increased life expectancy. Despite advances in early diagnosis and treatment, eradication involves therapies with numerous adverse effects during and after treatment. These include lymphedema, arthralgia, fatigue, osteoporosis, sleep disturbances, cardiotoxicity, peripheral neurotoxicity [1-3], and anxiety, fear, and depression (3).

As a result, these patients often experience poor quality of life and overall well-being (4). This concern has led to the exploration of new strategies to improve the lives of these patients, including both pharmacologic and non-pharmacologic interventions such as the recommendation of physical exercise (5-7).

Exercise is an accepted intervention to improve the quality of life of cancer patients due to its benefits in cardiovascular and muscular health and fatigue reduction (1-3). Its practice is safe and feasible at all stages of the oncological process (8), potentially reducing recurrence time, improving survival, and mitigating side effects of cancer treatments (9). Given these benefits, current guidelines recommend that physical activity be incorporated into the routine of cancer patients (8,10).

However, cancer patients often do not meet the minimum exercise guidelines (11), which recommend 150 minutes per week of moderate-intensity aerobic exercise (heart rate 30-80%) or 75 minutes per week of vigorous exercise (12-14), combined with strength training 2-3 times per week (15). Difficulty balancing daily routines, exercise, and medical appointments contributes to inadequate physical activity (16).

One of the main reasons for not exercising is the fear of causing harm or performing exercises that may be contraindicated in their health status (17). Therefore, it is recommended that physical activity be performed in structured programs guided by oncology professionals (18), which provides women with a sense of security and increases adherence (19). This aspect is crucial and challenging due to the scarcity of resources and trained personnel in the field of oncology.

Alternatives such as remote session monitoring have been shown to be a good alternative to traditional brochures (20) to reach a larger population. Participation in face-to-face group exercise programs has shown very satisfactory results in the quality of life of cancer patients (21). Recently, new modalities such as home-based exercise or booklets have been incorporated (22).

Since there are no studies comparing the three modalities of exercise prescription - in-person group, home-based exercise, and pamphlet prescription - this study aims to determine the effectiveness of three modalities of exercise prescription (in-person, home-based exercise, pamphlet prescription) on the quality of life of breast cancer patients actively undergoing treatment.

2. Materials and Methods

Design: Quasi-experimental study with randomized assignment to three groups (in-person: 24-week guided and supervised in-person exercise program; home-based exercise: 24-week guided and supervised exercise program with streaming monitoring; recommendation: exercise recommendation guided by informational booklet, with baseline and 6-month analyses from the start of the study. The study period was October 2021 to July 2023.

Population and setting: Women diagnosed with breast cancer (stage I-IV) actively undergoing treatment (chemotherapy, radiotherapy, hormone therapy). Exercise prescription should not be contraindicated by the oncologist, and participants must agree to participate in the study. Group assignment was based on group capacity (35 people per group) according to the group sequence: face-to-face - home-based exercise - referral. The estimated sample size was based on a 95% confidence level, a 5% margin of error, and a population of 105, resulting in a sample size of 80 patients. Recruitment was carried out at the Medical Oncology Service of the Provincial Hospital Consortium of Castellón. The study was conducted according to the Declaration of Helsinki,

approved by the Human Research Ethics Committee of the Castellón Provincial Hospital Consortium (Protocol dated January 29, 2020). Written informed consent was obtained from all participants prior to the study. The study, which currently lacks an identification code, has been registered on ClinicalTrials.gov. This code will be provided during the article review process.

Intervention: The intervention for each group consisted of a 24-week personal training program guided and supervised by a graduate in physical activity and sports, specialized in exercise and oncology. The sessions consisted of a 10-minute warm-up with joint mobility and balance exercises. This was followed by a 40-minute main exercise session to improve upper and lower body strength and cardiorespiratory fitness, focusing on all major muscle groups and using body weight, resistance bands and/or free weights, exercise mats, and materials available at home (plastic bottles, shopping bags, etc.). This portion included a combined circuit of 8-12 functional exercises (e.g., squats, front and side lunges, sit-ups, calf raises, glute bridges, core, biceps curls, shoulder presses, punches, jumping jacks, static walking/jogging). The circuit consisted of 2 sets of 10-12 repetitions for the functional strength exercises and 30 seconds for the aerobic exercises. Volume was progressively increased by modifying the number of repetitions and sets and the complexity of the exercises. A minimum rest period of 90 seconds was established between exercises. For home-based exercise, the synchronously supervised home-based group participated in a home-based exercise program streamed and supervised by their oncology team for 6 months. Participants were asked to complete a 60-minute combined resistance and aerobic exercise session two days per week for 6 months (24 weeks). The sessions were controlled, guided, and supervised by a cancer exercise specialist who encouraged and provided feedback to the participants while they could observe the performance, interact, or ask questions.

In the home-based exercise, Google Meet was used for the connection, using the teacher's and patient's cameras and microphones. The exercise program was guided and supervised via live streaming, with the same training plan as in the face-to-face group. Exercise prescription through weekly recommendations (informative booklet with types of exercises and descriptions of how to perform them) for the recommendation group. Attendance was monitored for the face-to-face and home-based exercise, with a minimum attendance of 70% of sessions.

Variables: Baseline (before group assignment) and 6-month analysis were performed on sociodemographic variables: age (years), marital status (married or in a relationship, separated or divorced, single, widowed), motherhood (yes or no), cohabitation (living alone or not), education level (primary, secondary, university), employment status (employed, unemployed, retired) and income (<1000 Euro, 1000 to 2000 Euro, >2000 Euro), clinical variables: tumor type (luminal A, luminal B (HER2+), luminal B (HER2), non-luminal, triple negative), treatment plan (adjuvant, neoadjuvant), laterality (right breast, left breast, bilateral), tumor stage (I, II, III, IV), chemotherapy (yes or no), radiotherapy (yes or no), hormone therapy (yes or no), and quality of life measured by the QLQ-C30 questionnaire (30 items): covering five cancer dimensions: physical functioning (items 1-5), daily activities (items 6 and 7), social (items 26 and 27), emotional (items 21-24), and cognitive (items 20 and 25). Three symptom scales: fatigue (items 10, 12 and 18), pain (items 9 and 19), nausea and vomiting (items 14-15). A global health scale (items 29-30) and individual items measuring disease and treatment symptoms: Shortness of breath (item 8), insomnia (item 11), loss of appetite (item 13), constipation (item 16), diarrhea (item 17), and financial impact (item 28). Likert-type response format, referring to a one-week period.

Statistical Analysis:

Statistical analysis was performed using IBM SPSS Statistics version 28 (IBM Corporation). The normal distribution of variables was verified by the Kolmogorov-Smirnov test ($p < 0.05$). As the variables were not normally distributed, non-parametric statistical tests were applied. To describe the collected data, we used the mean and standard deviation for continuous variables, and frequency for categorical variables. The bivariate analyzes (pre-post) of repeated measures were performed using the Wilcoxon test.

Multiple regression analysis was performed using the forward stepwise method. Only normally distributed variables were used as dependent variables. The parsimony principle was applied to the

models obtained (23). Given the limited sample size and the non-normal distribution of the independent variables, the residual errors of the resulting models were checked to ensure their normal distribution and thus the reliability of our regression models (24). To determine the predictive value of the model, the Cohen criterion was applied to one-way ANOVA models. This criterion indicates that R² values below 0.10 do not represent a relevant explanatory value, while R² values between 0.10 and 0.25 indicate a dependence of the explanation of the variance of the analyzed variable on the identified factors, and with R² values above 0.25 we can affirm that the explanatory model is very clinically relevant. Statistical significance is assumed at p-value <0.05.

To calculate the reliability of the data obtained, we calculated Chronbach's alpha in the total result of the Global Health Scale and in the dimensions (physical functioning, daily activities, emotional, cognitive).

3. Results

3.1. Sociodemographic description of the sample

A total of N=105 patients meeting the inclusion criteria were recruited, with study completion in the face-to-face group (n=21; 26.3%), home-based exercise group (n=31; 38.8%), and recommendation group (n=28; 35%). The total sample analyzed was n=80. See flow chart for reasons for dropout by group.

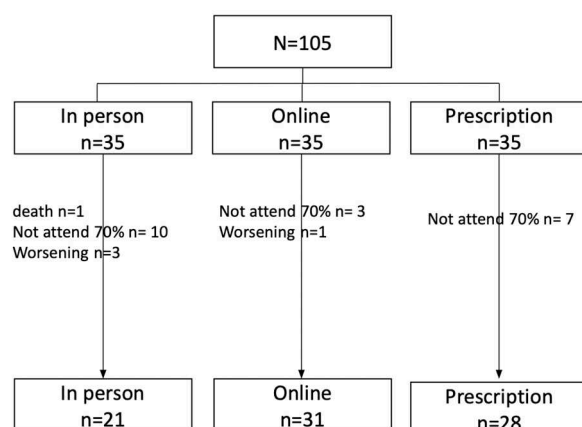


Figure 1. Flowchart of the process.

The mean age was 48.6 years, with married marital status (n=55; 68.8%), living with others (n=72; 90%), secondary education (n=35; 43.8%), employed (n=60; 75.5%), and income between 1000 and 2000 Euros (n=45; 56.3%), with no differences between groups according to allocation, see Table 1.

Table 1. Sociodemographic description of the sample.

	In person n (%)	Online n (%)	Prescription n (%)	Total n (%)
Age (mean±sd)	46.1±8.7	49.0±8.9	50.1±7.9	48.6±8.6
Marital Status				
Married or in a relationship	14 (66.7)	24 (77.4)	17 (60.7)	55 (68.8)
Separated or divorced	2 (9.2)	4 (12.9)	5 (17.9)	11 (13.8)
Single	3 (14.3)	2 (6.5)	6 (21.4)	11 (13.8)
Widowed	2 (9.5)	1 (3.2)	0 (0.0)	3 (3.8)

Motherhood (yes)	15 (71.4)	25 (80.6)	22 (78.6)	62 (78.5)
Cohabitation				
No live alone	18 (85.7)	30 (96.8)	24 (85.7)	72 (90)
Live alone	3 (14.3)	1 (3.2)	4 (14.3)	8 (10)
Education Level				
Primary	3 (14.4)	6 (19.4)	5 (17.9)	14 (17.6)
Secondary	9 (42.8)	12 (38.7)	14 (50.0)	35 (43.8)
University	9 (42.8)	13 (41.9)	9 (32.1)	31 (38.8)
Employment Status				
Employed	18 (85.7)	23 (74.2)	19 (67.9)	60 (75.5)
Unemployed	2 (9.5)	5 (16.1)	8 (28.6)	15 (18.8)
Retired	1 (4.8)	3 (9.7)	1 (3.6)	5 (6.3)
Income				
<1000 euros	5 (23.8)	13 (41.9)	8 (28.6)	26 (32.5)
1000 - 2000 euros	12 (57.1)	15 (48.4)	18 (64.3)	45 (56.3)
>2000 euros	4 (19.0)	3 (9.7)	2 (7.1)	9 (11.3)

3.2. Description of the clinical status of the sample

The most common tumor according to pathological anatomy was ductal carcinoma (n=77; 96.6%), in the left breast (n=42; 53.8%), in stage II (n=43; 53.8%). The treatment plan was adjuvant in 55 cases (68.7%), 47 patients (60.2%) received chemotherapy during the study. The most commonly prescribed treatments were radiotherapy (n=68; 85%) and hormonal therapy (n=68; 85%). No differences were observed between groups according to allocation, see Table 2.

Table 2. Description of the clinical status of the sample.

	In person n (%)	Online n (%)	Prescription n (%)	Total N (%)
Tumor Type				
Luminal A	7 (33.3)	12 (38.7)	10 (35.7)	29 (36.3)
Luminal B (her2 +)	3 (14.3)	4 (12.9)	5 (17.8)	12 (15.0)
Luminal B (her2 -)	9 (42.8)	11 (35.4)	10 (35.7)	30 (37.5)
Non luminal	1 (4.8)	2 (6.5)	2 (7.2)	5 (6.2)
Triple negative	1 (4.8)	2 (6.5)	1 (3.6)	4 (5.0)
Treatment plan				
Adjuvant	15 (71.4)	21 (67.7)	19 (67.9)	55 (68.7)
Neoadjuvant	6 (28.6)	10 (32.3)	7 (25.0)	23 (28.8)
Surgery only	-	-	2 (7.1)	2 (2.5)
Laterality				
Right breast	10 (47.6)	10 (32.3)	10 (35.7)	30 (37.5)
Left breast	9 (42.9)	17 (54.8)	17 (60.79)	43 (53.8)
Bilateral	2 (9.5)	4 (12.9)	1 (3.6)	7 (8.7)
Tumor stage				

I	5 (23.8)	9 (29.0)	13 (46.4)	27 (33.8)
II	11 (52.4)	20 (64.5)	12 (42.9)	43 (53.8)
III	3 (14.3)	1 (3.2)	1 (3.6)	5 (6.2)
IV	2 (9.5)	1 (3.2)	2 (7.1)	5 (6.2)
Treatment during the study				
Chemotherapy	14 (66.7)	16 (51.6)	17 (60.7)	47 (58.8)
Radiotherapy	2 (9.5)	4 (13.0)	2 (7.1)	8 (10.0)
Hormonotherapy	5 (23.8)	11 (35.5)	9 (32.2)	25 (31.2)
Prescribed treatment				
Chemotherapy	18 (85.7)	20 (64.5)	18 (64.3)	56 (70.9)
Radiotherapy	16 (76.2)	25 (80.6)	27 (96.4)	68 (85.0)
Hormonotherapy	18 (85.7)	25 (80.6)	25 (89.3)	68 (85.0)

3.3. Quality of Life Results

As shown in Table 3, global quality of life improved significantly at 24 weeks in the face-to-face and home-based exercise groups, but not in the recommendation group.

By dimension, quality of life worsened significantly (p -value <0.05) in activities of daily living (baseline=43.40; 24 weeks=37.67), social dimension (baseline=50.30; 24 weeks=44.84), and emotional dimension (baseline=47.91; 24 weeks=43.84).

For symptoms, significant improvements (p -value <0.05) were observed for fatigue (baseline=51.31; 24 weeks=46.49), nausea and vomiting (baseline=33.10; 24 weeks=26.86), loss of appetite (baseline=35.94; 24 weeks=26.92), and constipation (baseline=45.63; 24 weeks=33.33). In the recommendation group, there was a significant improvement in constipation (baseline=40.48; 24 weeks=29.76), in the home exercise group, there were significant improvements in nausea and vomiting (baseline=37.68; 24 weeks=27.42), appetite loss (baseline=39.52; 24 weeks=26.92), and constipation (baseline=50.81; 24 weeks=36.54). The recommendation group did not show statistically significant differences in any of the symptoms.

Table 3. Quality of life results.

	Groups	Basal	24 weeks	P Value/ d Cohen
Global Health				
	Total	70.63 (± 16.96)	77.25(± 14.29)*	$<0.001/0.53$
	In person	75.14 (± 13.26)	81.71(± 13.67)*	0.02/ 0.55
	Online	69.35(± 16.40)	77.27(± 13.83)*	0.005 / 0.60
	Prescription	68.64 (± 19.77)	72.95(± 14.72)	
Dimensions				
Physical Functioning	Total	34.01 (± 10.44)	34.20 (± 11.93)	
	In person	30.24 (± 6.01)	30.48(± 4.71)	
	Online	36.77 (± 12.01)	33.08 (± 10.87)	
	Prescription	39.09 (± 10.59)	33.75 (± 16.08)	
Daily Activities	Total	43.40 (± 19.92)	37.67 (± 16.28)*	
	In person	35.76 (± 14.41)	33.19 (± 12.78)	$<0.001/0.37$
	Online	47.32 (± 19.87)	37.54 (± 15.81)	0.014/ 0.47
	Prescription	44.79 (± 22.43)	42.09 (± 19.10)	

Social	Total	50.30 (±21.93)	44.84 (±22.94)*	0.018/0.35
	In person	50.76 (±22.85)	45.95 (±19.87)	
	Online	53.74 (±22.41)	47.69 (±23.98)	
	Prescription	46.14 (±20.75)	40.41 (±24.72)	
Emotional	Total	47.91 (±17.95)	43.84 (±18.26)*	0.014/0.26
	In person	53.43 (±16.54)	51.90 (±19.33)	
	Online	49.29 (±21.97)	39.73 (±15.41)*	0.019/0.53
	Prescription	42.25 (±13.68)	41.01 (±18.62)	
cognitive	Total	43.28 (±17.60)	43.09 (±18.67)	
	In person	41.76 (±15.43)	41.06 (±16.54)	
	Online	44.13 (±15.82)	42.04 (±17.33)	
	Prescription	45.59 (±22.37)	43.89 (±21.15)	
Symptoms				
Fatigue	Total	51.31 (±18.56)	46.49 (±14.61)*	0.007/0.31
	In person	47.14 (±14.27)	45.19 (±9.34)	
	Online	54.74 (±20.22)	45.54 (±14.07)	
	Prescription	50.64 (±19.37)	48.86 (±19.07)	
Pain	Total	46.69 (±19.20)	46.75 (±16.72)	
	In person	41.24 (±13.86)	43.67 (±14.62)	
	Online	52.52 (±22.44)	47.35 (±13.81)	
	Prescription	44.32 (±17.56)	49.01 (±31.42)	
Nausea and Vomiting	Total	33.10 (±12.74)	26.86 (±6.27)*	<0.001/0.52
	In person	30.43 (±9.39)	26.24 (±3.91)	
	Online	37.68 (±15.25)	27.42 (±8.75)*	0.009/0.71
	Prescription	30.04 (±10.58)	26.77 (±4.56)	
Shortness of breath	Total	30.94 (±12.73)	31.01 (±13.27)	
	In person	29.76 (±10.06)	29.29 (±10.52)	
	Online	33.06 (±16.31)	28.85 (±9.19)	
	Prescription	29.46 (±9.75)	35.23 (±18.35)	
insomnia	Total	53.75 (±25.50)	56.88 (±24.96)	
	In person	59.52 (±27.92)	63.10 (±23.21)	
	Online	54.84 (±26.94)	53.85 (±24.18)	
	Prescription	48.21 (±21.44)	54.55 (±27.43)	
Loss of appetite	Total	35.94 (±18.16)	28.99 (±11.03)*	0.005/0.32
	In person	33.33 (±12.07)	29.76 (±10.06)	
	Online	39.52 (±21.18)	26.92 (±6.79)*	0.013/0.55
	Prescription	33.93 (±18.27)	30.68 (±15.29)	
Constipation	Total	45.63 (±26.91)	33.33 (±16.42)*	<0.001/0.47
	In person	40.48 (±24.33)	29.76 (±12.79) *	0.002/0.45
	Online	50.81 (±29.21)	36.54 (±20.28)*	0.002/0.56

	Prescription	43.75 (±26.02)	32.95 (±14.19)	
Diarrhea	Total	31.25 (±15.15)	28.62 (±9.85)	
	In person	30.95 (±13.47)	28.57 (±8.96)	
	Online	29.03 (±9.35)	29.81 (±12.28)	
	Prescription	33.93 (±20.65)	27.27 (±7.35)	
Financial impact	Total	40.31 (±24.03)	41.30 (±24.94)	
	In person	34.52 (±18.50)	42.86 (±27.54)	
	Online	46.77 (±27.94)	44.23 (±25.79)	
	Prescription	37.50 (±22.04)	36.36 (±21.44)	

3.4. Reliability of the QLQ-C30

Reliability, based on the calculation of global Cronbach's alpha and by dimension, ranged from 0.762 to 0.906. See Table 4.

Table 4. Reliability Scale.

	Alfa de Cronbach
Global Health	0.898
Physical Functioning	0.762
Daily Activities	0.829
Social	0.906
Emotional	0.886
Cognitive	0.877

3.5. Regression analysis results.

QOL at 24 weeks depended on active chemotherapy, tumor type, and assigned exercise group, accounting for 50.3% of the variance ($r^2 = 0.503$; $p < 0.001$).

Table 5. Explanatory model of variance (regression).

Model	R2 Adjusted	Standard Error	F (p)
Dependent Variable: Global Health Scale at 24 weeks into the program Covariates: Tumor type. Chemotherapy and Type of physical exercise program	0.503	9.710	14.515(<0.001)

4. Discussion

The quality of life of breast cancer patients undergoing active treatment improves after a 24-week exercise program. These data support the importance of prescribing exercise during cancer treatment (1-3,8). Physical activity is particularly effective in improving quality of life when delivered in person and virtually. These results are likely due to the development and supervision of these sessions by specialists in physical activity and cancer (18), which is consistent with the results of the Heiman study (1), which showed significant improvements in quality of life in patients who received

guided and supervised exercise. Such supervision maximizes the benefits of exercise and helps women feel safe in their exercise routine (19).

In terms of dimensions, quality of life worsened significantly in the performance of activities of daily living, social dimension, and emotional dimension. No significant differences between the groups were observed in the analysis. Our results are not consistent with those of other researchers (21), who reported satisfactory results in improving QOL in all dimensions, both in home-based exercise prescription modalities (25) and in face-to-face sessions (5). Our results may be more related to changes in family and social dynamics after diagnosis than to the benefits of exercise prescription. Most research has been conducted in breast cancer survivors who have completed their oncologic treatment and have experienced life changes after cancer (2,5,9,10,12,13,26).

Exercise in all modalities improved important aspects such as fatigue, nausea, vomiting, appetite, and constipation-symptoms that often lead to treatment discontinuation or delay. The face-to-face group, and especially home-based exercise, showed greater benefits in reducing nausea, vomiting, appetite loss, and constipation. These factors make home-based exercise, streaming-based programs a resource to consider in exercise recommendation. Therefore, it is an alternative to offer guided and supervised exercise programs to a larger population, as confirmed by other researchers (26,27).

The confidence level obtained from the QLQ-C30 scale is 0.898, data higher than those obtained in its original validation with a confidence level of 0.846 (28). Although its validation was carried out in patients with breast cancer 6 and 12 months after the end of their treatments and based on the results of Aune's meta-analysis (7), they establish that this questionnaire is not adequate to reflect quality of life in the short term, since it presents a large variability of effect size when evaluated during treatment. Recommended questionnaires for assessing quality of life during treatment are the Functional Assessment of Therapy (FACT) questionnaire with its subscales of symptoms, physical well-being, and functional well-being, which have a Cronbach's alpha ranging from 0.55 to 0.76 (13). Values lower than those reported in

In conclusion, QoL is influenced by the type of treatment received during the trial, especially chemotherapy, which along with surgery (29) has the greatest impact on QoL-related symptoms, as well as tumor type. Luminal A breast cancer subtypes have a better prognosis after exercise (30). Therefore, the explanatory model is associated with known quality of life variables in breast cancer patients.

5. Conclusions

The quality of life of breast cancer patients undergoing active treatment improves after a 24-week exercise program, especially in programs designed and supervised in-person and home-based exercise. Home-based exercise using the streaming-based modality is a good option for exercise prescription.

Author Contributions: Conceptualization: Suárez-Alcázar MP., García-Roca E and Folch Ayora A.; Methodology: Folch-Ayora A; Formal Analysis, Collado-Boira, E; Investigation: Recacha-Ponce P, Temprado-Albalat MD, Hernando-Domingo C, García-Roca E, Sala-Medina P; Baliño-Remiro P, Muriach-Sauri M, Flores-Buils R; Data Curation: Collado-Boira E; Writing – Original Draft Preparation: Suárez-Alcázar MP and Folch Ayora A; Writing – Review & Editing, Collado-Boira E; Project Administration: Suárez-Alcázar, MP..

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Data Availability Statement: For ethical reasons related to the preservation of patient identity, the data presented in this study are available upon request to the corresponding author.

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