Manuscript title

Effect of exercise on phase angle in cancer patients: a systematic review

Running title

Phase angle in cancer patients

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Abstract

INTRODUCTION: Body composition is one of the main variables of interest in clinical practice in cancer patients. Specific markers from bioelectrical impedance analysis, such as phase angle (PhA), have been assuming increasing relevance in this population. The aim of the present systematic review was to study and systematise the effect of exercise on PhA in cancer survivors, as compared to control conditions, namely usual care, with no exercise. The effect of exercise on PhA in the population of cancer survivors is not yet established.

EVIDENCE ACQUISITION: This systematic review was conducted on October 13, 2021, through PubMed, Web of Science, Wiley Online Library, Directory of Open Access Journals, Science Direct and JSTOR, following PRISMA guidelines and PICOS model that include: cancer survivors with ≥18 years; intervention of any exercise program for the target group; comparison between intervention group and control group that followed control conditions, namely usual care, with no exercise; outcome related to PhA; and studies of randomized control trials.

EVIDENCE SYNTHESIS: We founded a total of 1244 publications, using selected keywords. Eight studies were included in this systematic review, after inclusion/exclusion criteria considered. Compared with the control conditions, exercise training programs seem associated with a positive effect on PhA, both in solid tumours and haematologic cancer types, but only when using resistance exercise alone. According to the best evidence synthesis criteria, we could not conclude the superiority of any exercise program analysed in the value of the PhA.

CONCLUSIONS: There were several exercise details that may have potential to be beneficial for PhA in cancer patients, including an early start of the exercise intervention (during treatment and immediately after discharge from hospital), the use of resistance exercise or/and aerobic exercise, and mainly a long follow-up period (≥ 4 months) to verify the structural effects of exercise on the PhA. However, there were no effects on the PhA value immediately after the intervention, regardless of the type of protocol and the intervention time.

Key words: Cancer patients, Phase Angle, Physical Exercise, Bioimpedance.

TEXT

Introduction

The 2020 Global Cancer Statistics mentions the occurrence of around 19.3 million new cancer cases and 10 million cancer deaths worldwide [1], which represents a major public health concern. One third of these deaths are due to five behavioural and nutritional risk factors, namely inadequate physical activity, high body mass index, low fruit and vegetable intake, and excessive tobacco and alcohol consumption [2]. Generally, weight and body mass index are used to characterise the physical and nutritional status of the adult population, however these parameters do not reflect the general health status of the population, namely in cancer patients' [3].

In this sense, body composition assessment, using bioelectrical impedance analysis (BIA), has received increasing interest for cancer patients' assessment in clinical practice [4]. This is not unrelated to the fact that this is an affordable, simple to use, non-invasive method, widely used for the assessment of body composition which has proven its usefulness for many years now [5].

BIA relies on the principle that different body tissues offer different levels of resistance to the passage of an electric current, so called impedance [6–8]. The impedance is the vector (Z) resulting from resistance (R) and reactance (Xc) [8,9]. The angle between the impedance vector and the X axis represents the phase angle (PhA) [7–9]. The PhA is suggested to reflect the integrity of cell membranes and been found to be related to body fluid distribution, functional capacity and nutritional status, therefore, it has been regarded as a marker of overall individual health status [10–12]. A low PhA seem to result from the loss of cell membrane integrity, and it is associated with poor health [11], which indicates impaired muscle function [12], while a higher PhA seems to result from higher cell vitality and better overall health [13] and it has been found in athletes and active persons [14,15]. Due to its' association with cell membrane integrity and overall health, including in persons with chronic diseases [16–18], PhA has been used in the clinical assessment of patients and diagnosis, in several clinical conditions, including cancer [4,16,19]. In healthy subjects PhA ranges from 5º to 7º [20] but in the population of cancer survivors, PhA has been found to range between 4º [21,22], and 5.5º [12,16], or 6º at 5 years post diagnosis [19] which lead to believe that cancer reduce the PhA values in general, even they meet sometimes the range values for healthy population. According to Hui et al. [23] an increase of 1º in PhA is associated with significant higher survival rates. This association was confirmed in another study that included different cancer types during treatment [24]. In this sense, a recently recent systematic review and meta-analysis suggested that PhA may be an important prognostic factor of survival in population of cancer [3] (23% less likely to survive than patients with high PhA values). Thus, it is necessary and fundamental to implement interventions in this population with the aim of increasing the value of this biomarker, which has recently been confirmed by other systematic review and meta-analysis where a cause-effect relationship between physical activity levels and PhA, independent of the type of physical activity and chronic condition reported was found [25].

Despite the evidence on the effect of exercise or physical activity on PhA, in the overall population, such effect on PhA in the population of cancer survivors is not yet established. Furthermore, to our knowledge, no specific recommendations nor guidelines regarding exercise prescription for the enhancement of PhA in cancer survivors were found which support the conduction of a systematic review to gather all information about exercise training programs and their effects on PhA. Thus, the aim of the present systematic review was to study and systematise the effect of exercise on PhA in cancer survivors, as compared to control conditions, namely usual care, with no exercise.

Methods

Study selection procedure

This study was conducted following the items of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [26]. Accordingly, the PICOS model was used to design and conduct this systematic review [27], as follows: P (patients) – cancer survivors with ≥ 18 years; I (intervention) – any exercise program intervention for the target group (e.g. strength training, resistance training, aerobic training, suspension training or others); C (comparison) – comparison between intervention group (IG) and control group (CG) that followed control conditions, namely usual care, with no exercise; O (outcome) – PhA assessed from electric bioimpedance analysis, as primary or second outcome; S (study) – randomized control trials. The primary outcome of this review was PhA, regarded as a cell health marker. Trials were excluded if: 1) home-based exercise was used in the whole intervention period; 2) they involved mixed cancer survivors without specific information on cancer survivors' results; 3) they did not include or report results regarding PhA; 4) they were written in a language other than English, Portuguese, and Spanish. Eligibility was assessed independently evaluated in duplicate, with differences resolved by consensus.

The search was conducted using the following electronic databases: PubMed, Web of Science (WoS), Wiley Online Library, Directory of Open Access Journals (DOAJ), Science

Direct, JSTOR, and included studies published until October 13, 2021, using the terms: (“phase-angle” OR “bioimpedance” OR “electrical impedance”) AND (“exercise” OR “physical activity” OR “training” OR “exercise program” OR “intervention”) AND (“cancer” OR “survivor” OR “neoplasm” OR “tumour” OR “secondary lymphedema”) (Table 1).

Data extraction

All articles identified by the search strategy underwent an evaluation of the titles and abstracts, in duplicate, by two assign researchers. All studies that were off the PICOS framework as outlined for this systematic review were excluded. Abstracts that did not provide sufficient information regarding the inclusion and exclusion criteria were selected for full-text evaluation. In a second phase, the same two assigned researchers independently evaluated all selected full-text articles and conducted a second selection in accordance with the inclusion and exclusion criteria. Disagreements between reviewers were solved by consensus in a meeting with a third researcher present. Data extraction from the selected full text articles was conducted by both assign researchers independently, using a list of intended data: i) first author; ii) year of publication; iii) target group (n) – patients; iv) sample size; v) sample age; vi) intervention details – frequency, intensity, duration (weeks), and type of exercise; vii) type of cancer; viii) control group characteristics; ix) main PhA results.

Methodological quality assessment

The methodological study quality was performed using the Physiotherapy Evidence Database (PEDro) scale [28], known as a valid and reliable instrument to assess eligibility, allocation to groups, blinding of allocation, and comparison between groups at baseline and its outcomes. This scale comprises 11 questions with yes or no answers (yes= 1; no= 0), providing a total score which ranges between 0 (poor methodological quality) and 10 (excellent methodological quality). The first item of the scale does not refer to the methodological quality of the randomized controlled trials but rather its external validity, which is excluded from the total score.

Scores were obtained from the PEDro database and were therefore scored by independently, avoiding any potential bias of the authors. When a study was not available on the PEDro database, two authors independently (A.D.M. and J.S.) rated the risk of bias. Disagreements between authors were solved by consensus in a meeting with a third author present (R.O.).

Level of evidence

Based on the physiotherapy evidence database scale and in order to assess the evidence of the interventions, the Van Tulder criteria [29] were applied, where the selected studies were grouped by levels of evidence, according to their methodological quality. A study with a physiotherapy evidence database score of 6 or more, is considered level 1 (high methodological quality) (6–8: good, 9–10: excellent) and a score of 5 or less is considered level 2 (low methodological quality) (4–5: moderate; <4: poor).

Due to the clinical and statistical heterogeneity of the results, a qualitative review was performed conducting a best-evidence synthesis [30,31]. This classification indicates that if the number of studies displaying the same level of evidence for the same outcome measure or equivalent is lower than 50% of the total number of studies found, no evidence can be concluded regarding any of the methods involved in the study.

Results

Studies included

A total of 1244 studies were retrieved from the selected databases (n= 6), using the selected keywords. These studies were then exported to reference manager software (EndNoteTM 20.0.1, Clarivate Analytics, Philadelphia, PA, USA). After removing duplicates, a total of 835 were retained form screening. After further selections screening 740 studies were excluded. Accordingly, 95 studies were retained for further eligibility assessment. A total of 8 studies were considered eligible and 87 were excluded for not meeting eligibility criteria (Figure 1).

With the exception of ~~one~~ two studies [32,33], all studies [34–39] were randomized controlled trials. The exception was a non-randomized controlled trial [32] and a pilot study which preliminary results will be confirmed in a randomized controlled trial approved by the Institutional Review Board [33].

Patients' characteristics

Table 2 shows characteristics of the patients included in this systematic review, namely country, age, type of cancer and treatment performed, fat free mass, fat mass and body mass index. The 8 studies included in the present systematic review, together, reported data of 340 cancer survivors, with an average age of 59.87 ± 8.29 years (n=192 were male, 56.47%). Studied patients had a diagnosis of one of the following cancer types: colorectal cancer (n=54, 15.88%); leukemia (n=53, 15.59%); breast cancer (n=49, 14.41%); esophagus cancer (n=42, 12.35%); lung cancer (n=40, 11.76%); pancreas cancer (n=21, 6.18%); prostate cancer (n=17, 5.0%); stomach cancer (n=14, 4.12%); ovary cancer (n=7, 2.06%); liver cancer (n=4, 1.18%);

head and neck cancer (n=4, 1.18%); bile cancer (n=3, 0.88%); and others cancers (n=32, 9.41%). Reported cancer stages included stage 1 (n=21, 6.18%), stage 2 (n=11, 3.24%), stage 3 (n=62, 18.24%), stage 4 (n=97, 28.53%) and no stage information (n=149, 43.82%). Exercise interventions were undertaken in patients during treatment (4 studies; n=135, 39.71%) or post-treatment (4 studies; n=206, 60.59%).

Exercise program characteristics

Table 3 presents characteristics of the interventions included in this systematic review. All 8 studies included in this review used different exercise prescription features, namely: frequency ranged from 2 [32,37,39] to 6 [37] weekly sessions and duration ranged from 10 [36] to 90 [38] minutes per exercise session. Moreover, different exercise program's intensities, particularly regarding the unit of measurement (percentage of maximal heart rate [33,34] vs percentage of heart rate reserve [37] vs rate of perceived exertion [33–36,38]) were used.

From all studies included, only one did not conduct an intervention with resistance exercise (RE) [39], however, the type of exercise approaches also varied between studies: two studies included both RE and aerobic exercise (AE) in the same exercise group [35,37]; one study included two intervention groups: one did RE and the other did AE [34]; two studies used RE alone, combined with synergic approaches: one used RE combined with muscle electrostimulation [32] and the other used RE combined with vibration platform [36]. Most of the interventions were properly supervised by exercise professionals [32–34,36,39], however, some studies did not supervise the entire intervention [35,37,38].

Exercise effects on PhA

Main PhA results of the reviewed studies are shown in Table 4. Exercise resulted in no changes on PhA from baseline in all intervention groups, regardless of the studied intervention and patients' specificities. Comparisons between the IGs and CGs also showed no differences in PhA, except in two studies [33,36] when comparing the IGs and CGs at the end of follow-up. In Pahl's study [36] the intervention occurred during cancer treatment (hospital stay) and included resistance training, five times per week, using a Vibration platform as a synergic approach to RE. In this study the IG despite having lower values than baseline as assessed immediately after the intervention and cancer treatment, showed near baseline values after 6-months follow-up, unlike the CG whose PhA results remained significantly lower than baseline even after the follow-up period ($p \leq 0.01$). In the same sense, Nusca et al. [33] showed significant differences between IG and CG after 4-months follow-up ($p = 0.022$). In this study, participants in the IG had higher values compared to the CG at baseline, but not significantly (p= 0.460), which was maintained after the 8-week exercise intervention (participants performed 4 weeks of AE and 4 weeks of AE with RE) (p= 0.141).

According to the best evidence synthesis criteria, we could not conclude the superiority of any exercise program analysed in the value of the PhA.

Risk of bias assessment

The methodological quality of the 8 studies included can be found in Table 5. The 8 studies obtained a score of between 3 [32,35] and 7 [37,39] on the PEDro scale. From all studies reviewed, 3 studies presented high methodological quality [level 1] [37–39], and 5 studies showed low methodological quality [level 2] [32–36]. Furthermore, the results of the PEDro scale revealed that one study did not specify the inclusion and exclusion criteria [34], 2 studies did not randomly allocation the participants into groups [32,33], 4 studies did not perform the allocation the participants into groups in a concealed way [32–35], and all studies included were similar at baseline. Additionally, none of the studies included blinded the participants and the professionals responsible for the program's sessions, 2 studies blinded the assessors who measured at least 1 key outcome [37,39], 4 studies could not perform assessments on at least 1 key outcome from more than 85% of subjects [32,34–36], all studies did not perform an intention-to-treat analysis, only one study did not report a between-group statistical comparisons for at least one key outcome [35], and finally, all studies reported both point measures and measures of variability for at least one key outcome.

Discussion

The present review aimed to study and systematised the effect of exercise on PhA in cancer survivors, as compared to control conditions, namely usual care, with no exercise. The main findings of this systematic review were: a) there were no effects on the value of the PhA immediately after the intervention, regardless of the type of protocol and the intervention time; and b) there were effects on the value of the PhA after the follow-up period (≥ 4 months), thus possibly a chronic adaptation to exercise.

A low PhA is associated with reduced life expectancy in cancer survivors [3,40] and several studies have reported higher life expectancy for those that present a PhA higher than 5.6º [23,41,42]. All studies included in the present systematic review report PhA results below 5.6º [32,34–39], except for one study [33] which showed a value of 5.6º in the IG at baseline and a value of 5.8º after 4 months from the end of the exercise program. The clinical relevance of the assessment of PhA have been underscored [20,43,44], namely due to the inverse association of PhA with relevant clinical outcomes such as cardiovascular disease [45] and length of hospital stay [23]. Recently, Martins et al. [12] showed that breast cancer survivors with higher PhA values have a higher intracellular water (ICW) values and consequently a better preservation in the extracellular water ECW/ICW ratio which reinforces a good quality and integrity of the cell membrane. Furthermore, PhA has been found directly related with survival and quality of life [41,46,47], and has been acknowledged as a marker of muscle function [16,47] and, therefore, may affect clinical decisions regarding treatment [48] and nutrition [49]. Accordingly, this line of research warrants further work from the scientific community [3,25].

Interventions with ~~E~~ exercise programs has been thoroughly endorsed as an important component of cancer treatment, in pre-habilitation, neoadjuvant and rehabilitation settings [50–52], particularly supervised exercise [53,54], but the effect of exercise in PhA values in the population of cancer survivors has been scarcely studied and is not yet established, particularly in more advanced stages of the disease in which there is often a marked muscle mass loss [55,56] and for whom this marker seems particularly critical [57]. Several studies have reported the important contribute of exercise for cell membrane integrity and vitality, particularly in the long term, when a structural effect may be observed (chronic adaptation to exercise) [7,36,52]. Exercise is also a known stimulus for increasing muscle mass and was found to promote increase in intracellular water [58,59], which has a positive effect on PhA [7,32]. In the present review, two studies showed effects on the PhA [33,36]. Interestingly, these effects occur at the end of the follow-up period in both studies. Pahl et al. [36] showed the potential for exercise to counteract long term negative effect of cancer disease and treatment on PhA, as shown by follow-up results, 6 month after treatment (PhA recovered to baseline values in the IG, but not in the CG), in the same sense, Nusca et al. [33] verified that IG showed significant improvements compared to the CG after 4 months from the end of the exercise program (in patients that underwent laparoscopic colorectal surgery) ($p = 0.022$). The authors note that this significant difference may be related to an increase in soft tissue mass and quality and cellular health, an idea that has been previously highlighted [60].

The studies included in the present systematic review comprise fairly different exercise programs, with considerable differences in exercise prescription components (Table 3). Regardless of acknowledged differences found in the exercise interventions between the reviewed studies, which make it challenging to compare results, a detailed analysis of the characteristics of the exercise interventions studied is key for identifying of promising roads for future research. From all studies reviewed, 7 included RE [32–38], with 3 of these reviewed studies using RE as a single mode of exercise[32,34,36], one of which also included AE in only one group [34]. The remaining 4 studies included both RE and AE, either in a periodized sequence [37,38] or alternated exercise approach [33,35], 3 of these studies [35,37,38] also resorted to unsupervised exercise, which has been shown to be ineffective for a number of outcomes [53,54], still not yet established for PhA. Finally, the most recent study [39] performed a Hatha Yoga exercise program, which is a branch of yoga. This approach focuses on general well-being through *pranayamas* (breathing control exercises), *asanas* (yoga postures), and *chanda* (meditation).

Exercise frequency ranged from 2 [37,39] to 6 [37] weekly sessions, which, in some cases exceeded the recommended frequency spectrum of either AE or RE for cancer patients [50,51]. Namely, O'Neill et al. [37] included up to 6 AE sessions per week, which exceeds the recommended 3 to 5, and Pahl et al. [36] included 5 RE sessions per week, which exceeds the upper limit of 3 sessions that have been recommended [50,51]. The Exercise and Sport Science Australia (ESSA) position statement for cancer management recognizes that benefits of exercise may be drawn from as little as 1 week RE session [51]. Exercise duration ranged from 12 [32] to 90 [38] minutes per exercise session and, considering combined exercise frequency and intensity, taking into consideration the reported data, only one study [33] is not within the recommended duration of 150 minutes per week of moderate exercise [50,52,54]. However, this study following other guidelines for cancer patients [61,62].

Broader discrepancies were found between exercise programs' intensities. Despite the fact, that AE and RE use different markers of intensity, each of the 5 reviewed studies that included AE used different AE intensity markers: percentage of maximal heart rate (%HRmax) [33,34]; percentage of heart rate reserve (%HRres) [37]; only heart rate [35]; and rate of perceived exertion (RPE) used with different scales, 0 to 10 [33,35,38] and 6 to 20 [34]. All these markers are endorsed for monitoring exercise intensity [51], but these discrepancies make it difficult to compare and discuss the obtained results. The fact that all 5 reviewed studies, using different approaches to AE, however, it is important to highlight the study by Nusca et al. [33] that found significant differences between IG vs CG for PhA ($p= 0.022$) after the follow-up period and between baseline and the follow-up period for IG in PhA ($p= 0.027$). This intervention had a high volume (about 180 min) and moderate intensity, with 3 exercise sessions per week. This intervention also chose to divide intervention into two phases, the first 4 weeks with only AE and the last 4 weeks with AE and RE. This approach should be applied in clinical practice in order to confirm these first results.

Even though, 7 studies included RE, some approaches also varied between studies: 4 studies included both RE and AE in the IG [33,35,37,38]; one study included two intervention groups: one RE group and AE group [34]; 2 studies used RE alone, combined with synergic approaches: one used RE combined with muscle electrostimulation [32], and the other used RE combined with vibration platform [36].

The studies that included a RE group with synergic approaches, in comparison with a CG, found a significant increase in skeletal muscle mass [32,36], which is related with PhA [47], however, only Pahl et al. [36] found a potential beneficial effect of exercise. Beyond the effects on PhA, both studies report relevant results, including an increase in ECW/ICW ratio in the CG, as compared with the IG (p= 0.008) [32]; an enhancement in the 6 minutes walking test in the IG, as compared with the CG (p= 0.046) [32], which has been reported to be determined by both cardiorespiratory fitness but also by lower limbs strength [63]; a reduction in symptoms, such as vomits and nausea, between baseline and the end of the intervention, in the IG only (p= 0.032), which are clinically relevant [32]; also a significant increase in peak oxygen consumption from baseline, in the IG (p= 0.035) [36]; and a better performance in countermovement jump in the IG as compared to the CG (p= 0.033) [36]. Such as we did previously with another study [33], it is important to highlight some aspects in the intervention of Pahl et al. [36]. This intervention had a frequency of 5 RE sessions per week, as compared to a frequency of 2 or 3 RE sessions per week found in the other studies (Table 4). The type of exercise used was also somehow singular, namely, was the only that used a vibration platform and used both dynamic and static RE [36], as compared to dynamic only exercise in the other studies. The results of this intervention seem to confirm that this exercise prescription facilitates physical recovery regarding the cardiorespiratory system, body cell mass, and PhA, which thus deserves application in clinical practice after surgery.

Regarding the study that carried out an exercise program Hatha Yoga [39], there were no significant differences in PhA after the intervention. The authors justified this result by the fact that the duration and intensity of the intervention was reduced.

Finally, it is important to highlight the safety and feasibility of the 3 interventions performed in a hospital setting [34,36,38] . Thus, these interventions require qualified exercise professionals to work with this population, because due to the intensity of the treatments (e.g., chemotherapy) the patients' physiological conditions have a great variability (e.g., blood values), so the prescribed exercise protocol (e.g., intensity, number of sets or repetitions) must be adjusted whenever justified.

Conclusions

Regardless of the diversity of exercise approaches tested, there were several exercise details that may have potential to be beneficial for PhA in cancer patients, including an early start of the exercise intervention (during treatment and immediately after discharge from hospital), the use of RE or/and AE, and mainly a long follow-up period (≥ 4 months) in order to verify the structural effects of exercise on the PhA. However, there were no effects on the PhA value immediately after the intervention, regardless of the type of protocol and the intervention time.

Still, due to the low methodological quality of the studies (best evidence synthesis criteria), this systematic review is exploratory and far from established and, for sure, warrants further research. The PhA is a clinically relevant marker and establishing sound guidelines regarding exercise for enhancing PhA and overall cellular health would greatly benefit cancer patients and related clinical practice.

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NOTES

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TABLES

Table 1: Research strategy used.

Search number	Research Content
#1	(((phase-angle) OR bioimpedance) OR electrical impedance)
#2	(((((exercise) OR physical activity) OR training) OR exercise program) OR intervention)
#3	((((((cancer) OR survivor) OR neoplasm) OR tumour) OR secondary lymphedema)
#4	#1 AND #2
#5	#1 AND #3
#6	#2 AND #3

Table 2: Characteristics of studies.

Reference	Country	Subjects by gender	Group (N)	Age (years)	Type of cancer	Type of treatment	Fat Free Mass (% or kg)	Fat Mass (% or Kg)	BMI (kg/m^2)
Eyigör et al. (2021)	Turkey	NR	CG – 16 IG – 15	CG – 50.7±7.6 IG –51.40±10.6	Breast	Surgery Chemotherapy Radiotherapy	NR	NR	CG – 24.5±3.4 IG – 26.0±4.9
Nusca et al. (2021)	Italy	7 M 4 F	CG – 5 IG – 6	CG – 73.0 IG – 63.5	Colon Rectal	Surgery	NR	NR	CG – 24.0 IG – 21.4
Storck et al. (2020)	Switzerland	29 M 23 F	CG – 25 IG - 27	CG – 64.2 ±9.2 IG – 62.0 ±11.4	Several, solid	Chemotherapy	NR	CG (Kg) – 24.7 ± 11.6 IG (Kg) – 26.4 ± 9.9	CG – 25.8 ±4.9 IG – 25.0 ± 4.6
Mascherini et al. (2020)	Italy	4 M 2 F	CG – 3 IG – 3	72.9 ± 7.3	Colorectal	Surgery	CG (Kg) – 54.3 ± 13.0 IG (Kg) – 54.7 ± 8.5	CG (%) – 25.2 ± 5.1 IG (%) – 30.8 ± 10.6	CG – 24.3 ± 2.7 IG – 30.1 ± 7.3
Pahl et al. (2020)	Germany	30 M 14 F	CG – 23 IG – 21	CG – 56 IG – 55	Several, hematologic	Surgery	CG (%) – 65.8 IG (%) – 63	CG (Kg) – 17.7 IG (Kg) – 22.7	CG – 26 IG – 26.1
Wehrle et al. (2019)	Germany	13 M 9 F	CG – 8 IG – 6 IG – 8	CG – 50.6 IG – 47.4 IG – 47.7	Leukemia	Chemotherapy	NR	NR	NR
O´Neill et al. (2018)	Ireland	35 M 8 F	CG – 14 IG – 16	CG – 64.14 ± 10.46 IG – 67.19 ± 7.49	Esophagic	Surgery Chemotherapy	CG (Kg) – 53.01 ± 15.91 IG (Kg) – 50.11 ± 18.22	CG (Kg) – 21.81 ± IG (Kg) – 22.77 ± 11.04	CG – 25.27 ± 4.83 IG – 25.69 ± 4.02
Schink et al. (2018)	Germany	74 M 57 F	CG – 35 IG – 96	CG – 59.1 ± 11.6 IG – 60.3 ± 13.1	Several, solid	Chemotherapy Radiotherapy Chemoradiation Targeted therapy Hormonal therapy	NR	CG (%) – 29.9 ± 8.6 IG (%) – 29.6 ± 7.5	CG – 25.5 ± 5.2 IG – 24.9 ± 3.8

Abbreviations: CG, control group; IG, intervention group; N, number; M, male; F, female; Kg, kilograms; %, percent; BMI, body mass index; NR, not reported; m, meters.

Table 3: Description of the interventions performed in the studies.

Reference	Exercises performed (n/session)	Intervention time (weeks)	Equipment	Exercise type	Frequency (times/week)	Intensity	Sets /exercise (n)	Reps per set (n)	Time (min/session)	Supervised?
Eyigör et al. (2021)	**7**	10	NA	Hatha Yoga	2	NR	NA	NA	60	Yes
Nusca et al. (2021)	RE 2	8	AE Stationary Bicycle or Treadmil	4 weeks (AE) 4 weeks (AE+ RE)	3	AE 60-70% HRmax 0 to 10 RPE scale RE 30–50% of predicted 1-RM (Brzycki formula) 0 to 10 RPE scale	2	10	60	Yes
Storck et al. (2020)	NR	12	Bicycles-ergometers or on treadmills – At the hospital	CT (AE + RE+ balance + coordination)	3 (2 training sessions were performed at the hospital and 1 training session was performed at home)	AE 4 to 6 from 0-10 RPE scale When patients were receiving chemotherapy the same day, the intensity was set to 3 from the RPE scale RE 4 to 5 from 0-10 RPE scale	3	10 – 15	90 – First session at the hospital 60 – Second session at the hospital NR – session at home	Yes – At the hospital No – At home
Mascherini et al. (2020)	8	AE 4 weeks discharge RE 25 after discharge	NR	CT (AE + RE)	3	HR 0 to 10 RPE scale	3	12	30	Yes – RE No – AE
Pahl et al. (2020)	5	4 – 6	Whole body vibration	RE with vibration platform	5	14 to 16 from 6-20 RPE scale	1	Reps with time (2 min)	10 – 20	Yes
Wehrle et al.	4 – 6	4 – 8	AE	AE and RE	3	AE	Were adapted using the RPE scale		30 – 45	Yes

(2019)			Stationary Bicycle or Treadmil RE Dumbbells and elastic bands			60-70% HRmax 12 to 14 from 6-20 RPE scale RE 12 to 14 from 6-20 RPE scale				
O´Neill et al. (2018)	2 and 6 exercises	12	AE Treadmill walking, stationary cycling RE Free weights and TheraBands	CT (AE + RE)	2 – 6	AE Low intensity (30%–45% HRres), progressed to moderate intensity (45%–60% HRres) RE All sets performed to fatigue (RM)	2 – 6	12 – 17	20 – 35	Yes and No
Schink et al. (2018)	7	12	Whole-body electromyosti mulation	RE + electro- stymulation	2	Frequency of 85 Hz and a pulse width of 350 µs inducing a 6 s muscle stimulation followed by a 4 s resting time	6	1	12 – 20	Yes

Abbreviations: AE, aerobic exercise; RE, resistance exercise; CT, combined training; HR, heart rate; HRmax, maximum heart rate; HRres, reserve heart rate; RPE, rating of perceived exertion; s, seconds; min, minutes; n, number; NR, not reported; RM, repetition maximum; NA, not applicable.

Table 4: Main results for PhA of the studies.

Reference	Aim (s)	Main Result (PhA)					
		Group (n)	**Pre (M ± SD)**	**Post (M± SD**	***P-value***	***P-value* (between CG vs IG at post)**	**Effect size**
Eyigör et al. (2021)	To examine the effects of Hatha yoga on PhA, body composition, and quality of life in patients with breast cancer.	CG (n= 16)	5.2±0.4	5.2±0.5	0.935	0.760	NR
		IG (n= 15)	5.2 ± 0.7	5.2±0.5	0.959		
Nusca et al. (2021)	To examine the effects of a post-operative combined and supervised physical exercise training on the quality of life and functional and nutritional parameters of patients that underwent laparoscopic colorectal cancer surgery, compared to usual care alone.	CG (n= 5)	4.6 ± NR	5.0 ± NR	0.786	0.141	NR
		IG (n= 6)	5.6 ± NR	5.6 ± NR	0.109		
Storck et al. (2020)	To examine the effect of a leucine-rich supplement in combination with nutrition and physical exercise on physical function, nutritional status, dietary intake, fatigue, quality of life and clinical course in advanced cancer patients.	CG (n= 25)	5.1 ± 0.7	5.06 ± NR	NR	0.391	NR
		IG (n= 27)	4.9 ± 0.8	4.98 ± NR	NR		
Mascherini et al. (2020)	To verify the effectiveness of an exercise program, in terms of functional and body composition parameters, after laparoscopic resective colorectal cancer surgery.	CG (n= 3)	4.3 ± 0.8	4.3 ± 0.7	> 0.05	> 0.05	NR
		IG (n= 3)	4.6 ± 0.4	4.5 ± 0.2	> 0.05		
Pahl et al. (2020)	To examine a promising exercise method on physiological and psychosocial capacities in patients during alloHCT.	CG (n= 23)	5.2 ± NR	4.7 ± NR	≤ 0.01	> 0.05	NR
		IG (n= 21)	5.3 ± NR	4.8 ± NR	≤ 0.01		
Wehrle et al. (2019)	To investigate independent effects of endurance and resistance training on physical capacity and quality of life in patients with acute leukemia during induction chemotherapy.	CG (n= 8)	5.5 ± NR	-1.84[&]	0.917	0.758	NR
		IG_{AE} (n= 8)	5.7 ± NR	-1.30[&]	0.123		
		IG_{RE} (n= 6)	4.8 ± NR	-1.40[&]	0.223		

O´Neill et al. (2018)	To evaluate the efficacy of a 12-week multidisciplinary program to increase the cardiorespiratory fitness, body compositions and health-related quality of life of esophagogastric cancer survivors.	CG (n= 14)	4.9 ± 1.28	4.92 ± 0.51	NR	0.302	0.04
		IG (n= 16)	4.8 ± 0.60	4.75 ± 0.72	NR		
Schink et al. (2018)	To examine the effect of a combined approach of the novel training method whole-body electromyostimulation (WB-EMS) and individualized nutritional support on body composition with primary focus on skeletal muscle mass in advanced cancer patients under oncological treatment.	CG (n= 35)	4.5 ± 0.7	NR	NR	0.320	NR
		IG (n= 96)	4.5 ± 0.8	NR	NR		

Abbreviations: PhA, phase angle; CG, control group; IG, intervention group; : AE, aerobic exercise; RE, resistance exercise; NR, not reported; [&], data are presented as standardized phase angle.

Table 5: Score on the methodological quality of the studies according to the Physiotherapy Evidence Database (PEDro) scale.

Reference	PEDro Scale											Total score	Methodological quality
	1	2	3	4	5	6	7	8	9	10	11		
Eyigör et al. (2021)	1	1	1	1	0	0	1	1	0	1	1	**7**	**Good**
Nusca et al. (2021)	1	0	0	1	0	0	0	1	0	1	1	**4**	**Moderate**
Storck et al. (2020)	1	1	1	1	0	0	0	1	0	1	1	**6**	**Good**
Mascherini et al. (2020)	1	1	0	1	0	0	0	0	0	0	1	**3**	**Poor**
Pahl et al. (2020)	1	1	1	1	0	0	0	0	0	1	1	**5**	**Moderate**
Wehrle et al. (2019)	0	1	0	1	0	0	0	0	0	1	1	**4**	**Moderate**
O´Neill et al. (2018)	1	1	1	1	0	0	1	1	0	1	1	**7**	**Good**
Schink et al. (2018)	1	0	0	1	0	0	0	0	0	1	1	**3**	**Poor**

Abbreviations: 1, Eligibility; 2, Random allocation; 3, Concealed allocation; 4, Baseline comparability; 5, Blind subjects; 6, Blind therapists; 7, Blind assessors; 8, Adequate follow-up; 9, Intention-to-treat analysis; 10, Between-group comparisons; 11, Point estimates and variability; Y, yes; N, No.

Note: Eligibility criteria item does not contribute to total score.

TITLES OF FIGURES

Figure 1: Flow chart of study design by PRISMA.