REVIEW

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Association of Handgrip Strength with Quality of Life in Breast Cancer Survivors: A Systematic Review and Meta-Analysis

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Abstract

Objective: Handgrip strength (HGS) is an indicator of general muscular strength and in cancer patients acts as a relevant marker associated with mortality and health. This study aimed to evaluate the association between peripheral muscle function and health-related quality of life (HRQoL) in breast cancer (BC) survivors. **Methods:** Systematic review registered on PROSPERO under number: CRD 42021225206. The searches were carried out on MEDLINE via Pubmed, PEDro, Cochrane Library, Embase, CINAHL via EBSCO and Science Direct databases. Observational studies evaluating the association between handgrip strength (HGS) and HRQoL in adult female BC survivors were included. No linguistic or time restrictions were applied. Two reviewers reviewed full texts for inclusion and performed data extraction and risk of bias using the Newcastle and Ottawa scale (NOS). **Results:** Five articles were included and involved 587 patients, mean age of 47 to 59 years. The percentage of decreased HGS ranged from 38.3% to 60.3%. HGS was associated with different quality of life measures. From meta-analysis including 220 patients, the correlation coefficient between HGS and HRQoL was 0.26 (95% CI: 0.07-0.35). **Conclusions:** Breast cancer survivors face decline of HGS. In this population HGS was correlated with HRQoL. However, more evidence are necessary.

Keywords: Muscle strength- hand strength- breast neoplasm- clinical evaluation- quality of life indicators

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Introduction

Breast cancer (BC) is the most common malignancy in women worldwide, and is the leading cause of cancer related-deaths in women (Bray et al., 2018). Although scientific and technological advancements have enabled the early diagnosis and timely treatment of BC, many women experience the adverse effects of the disease and complications in treatment, which eventually affect their health-related quality of life (HRQoL) negatively (Annunziata et al., 2018).

With the increase in survival and life expectancy of women with BC, the HRQoL has become an even more important therapeutic target (Koniecznyet al., 2020). This is because the QoL of cancer survivors is lower than that of individuals without cancer, thus demonstrating the need for monitoring and interventions (Schmidtet al., 2018).

The various treatments for BC (surgery, chemotherapy, radiotherapy, targeted therapy, and hormone therapy) have several consequences, including a negative effect on muscle function, resulting in fatigue and sarcopenia and leading to a poorer QoL for BC survivors (Guigni et al., 2018; Klassen et al., 2017). Although BC is not typically characterized by cases of cachexia (Guigni et al., 2018), muscle strength is a primordial component in the physical examination of these patients, and should be included as a therapeutic objective in care protocols to better direct recovery and rehabilitation strategies, thus minimizing the adverse effects of declining muscle function (Cantarero-Villanueva et al., 2012).

Handgrip strength (HGS) is an indicator of general muscular strength that has been widely used in clinical evaluations and scientific research because of its practicality and low cost (Bohannon, 2019; Jochemet al., 2019). Previous studies have demonstrated the capability of HGS in cancer patients as a marker of clinical and nutritional status (Keaver et al., 2021), a predictor of decreased functionality and functional capacity (Duarteet al., 2020; Perez et al., 2018; Rijket al., 2016), and as a predictor of worse HRQoL and mortality in BC patients (Cantarero-Villanueva et al., 2012; Duarte et al., 2020; Paek and Choi, 2019b; Zhuang et al., 2020). However, the evidence regarding the predictive power of HGS in the HRQoL of BC survivors is not well delineated. In this context, this systematic review aimed to evaluate the association between HGS and HRQoL in women with BC.

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Material and Methods

A systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Page et al., 2021). The review protocol was registered in the Prospective Register of Systematic Reviews (PROSPERO): CRD 42021225206.

For this review, transversal observational or cohort studies (prospective or retrospective) that analyzed the association between HGS and HRQoL in women BC survivors were deemed eligible. Studies where HGS was evaluated using a manual dynamometer and HRQoLHRQ through a validated questionnaire were included. Studies that did not present isolated data on the association between the outcomes HGS and HRQoL, as well as conference abstracts, were excluded. No restrictions were imposed in terms of the date or language of publication.

The search for the articles was performed on August 18, 2021 by D.D. in MEDLINE via the Pubmed, PEDro, Cochrane Library, Embase, CINAHL EBSCO, and Science Direct databases. The search strategy involved keywords combined by boolean operators as follows: (breast cancer OR breast tumor OR breast cancer) AND (handgrip OR hand strength) AND (quality of life) AND (association OR correlation OR relationship) AND (cross-sectional study OR observational study). Studies obtained from other sources or article references, provided they met the eligibility criteria, were also included.

Selection process

After identification of the citations in the databases, we proceeded with the removal of duplicate entries through Mendeley software (Elsevier Inc., USA, New York). The screening of articles was performed based on reading the title and abstract by two independent reviewers (A.C.C.S. and C.M.A.). In the next step, the reviewers evaluated the studies through a full reading, and proceeded with the application of the eligibility criteria. Disagreements were resolved by a third researcher (D.D.).

Agreement between the reviewers was measured using the Kappa coefficient, and the values were interpreted as no to slight (0.01–0.20), reasonable (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80), and near perfect (0.80–1.00) agreement (McHugh, 2012).

The primary endpoint of this review was the association between HGS and HRQoL, while the secondary endpoint was HGS deficit, which was calculated by the difference in HGS between the affected and non-affected sides.

Data extraction

The articles included were reanalyzed and the relevant data were extracted by the two reviewers using an electronic spreadsheet. The primary studies collected data on authorship, country where the study was conducted, year of publication, sample size, mean age of participants, protocol used to measure HGS, forms of QoL evaluation, type of association analysis between variables, and main results.

Methodological quality assessment

The Newcastle-Ottawa scale (NOS) was used to assess the quality of the articles included (Stang, 2010). The NOS is based on a star rating system, and a maximum of 9 stars can be attributed to each study (for prospective and cross-sectional studies). The quality assessment was independently verified by two authors, and any disagreements were resolved by a third reviewer. The studies that received a score equal or higher than 7 were considered of high quality (Bae, 2016).

Statistical analysis

R software (version 4.2.1) was used for meta-analysis of correlation. The meta-analysis method involved the inverse variance method, restricted maximum-likelihood estimator for tau^2, and Fisher's z transformation of correlations. The studies that reported correlation coefficient (r value) were pooled in different analysis, considering the total score or quality of life questionnaire domains which are comparable with each other. The heterogeneity of studies was assessed by the Q-statistic and I^2 statistics. For studies heterogeneous (I^2>50%) the effect size was determined by random effects model. Otherwise, common effects model was used. Funnel plots were used to determine publication bias.

Results

A total of 178 studies were identified, of which 37 duplicate entries were excluded. Of the 11 studies selected for full reading, the most common reason for exclusion was not presenting association data between HGS and HRQoL. In addition, two studies were congress abstracts and the full versions were not available, one study evaluated HGS in another population, and one study was excluded because it was a systematic review. The process is detailed in Figure 1. The screening process showed substantial inter-rater agreement (k = 0.677).

Characteristics of the studies

The five articles included in this review (Brandini et al., 2019; Buyukakincak et al., 2014; Esteban-Simón et al., 2021; Kaya et al., 2010; Koca et al., 2020) have a cross-sectional design and involved a total of 587 women BC survivors who were mostly recruited from Turkey (Buyukakincak et al., 2014; Kaya et al., 2010; Koca et al., 2020) with a mean age >50 years. The characteristics of the studies are summarized in Table 1.

Of the studies included, only the study by (Buyukakincak et al., 2014) evaluated patients in the immediate postoperative period of mastectomy for BC. The other studies included patients who were in adjuvant treatment or had concluded systemic treatments for cancer. Patients with lymphedema were also included in the studies.

The performance of bilateral mastectomy was an exclusion criterion for most studies (Brandini da Silva et al., 2019; Buyukakincak et al., 2014; Kaya et al., 2010; Koca et al., 2020). In the study by (Esteban-Simón et al., 2021) there was no information regarding this exclusion criterion. In all studies, participants with previous shoulder or musculoskeletal problems in the upper limbs were excluded.

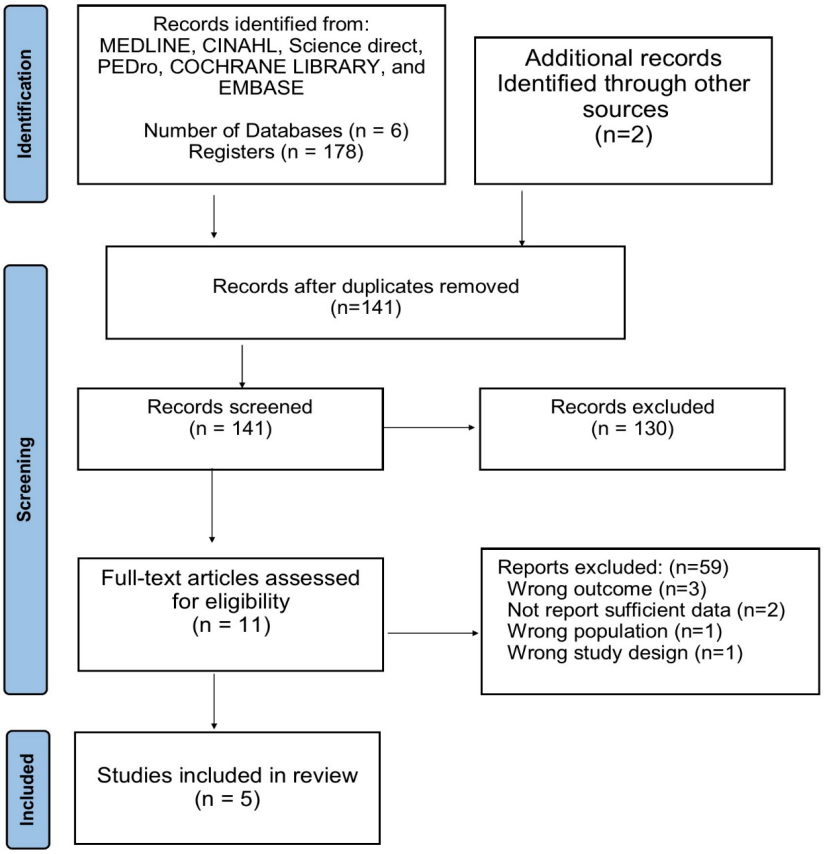

Figure 1. Flowchart of Systematic Review Selection

HGS measures

All measurements of HGS were performed with the use of a dynamometer. In two studies (Buyukakincak et al., 2014; Koca et al., 2020) the Jamar model dynamometer was used; one study (Brandini da Silva et al., 2019) used a Saehan model SH50 dynamometer; another used a digital (Esteban-Simón et al., 2021) used a digital dynamometer, model TKK 5401 Grip-D; and one study (Kaya et al., 2010) did not specify the brand.

In most studies, (Brandini da Silva et al., 2019; Buyukakincak et al., 2014; Kaya et al., 2010; Koca et al., 2020) the HGS was measured in both hands and the protocol involved the performance of three measurements for each side with registration of the mean value obtained. In the study by Esteban-Simón et al., (2021) two attempts were made on each hand in an alternating manner, and the best result for each was selected. In addition, in this study the authors used the HGS in absolute and relative form, which consists of the absolute value of the HGS of both hands divided by the body mass index (BMI).

Three studies reported data on HGS deficit of the evaluated patients. In two studies (Buyukakincak et al., 2014; Kaya et al., 2010) a value equal or greater than 10% of difference in HGS between the affected and non-affected side was considered as HGS impairment. For (Brandini da Silva et al., 2019) the cut-off point was an alteration between the limbs of 12%.

Assessment of HRQoL

HRQoL was evaluated using different validated instruments: Breast Cancer Treatment Outcome Scale (BCTOS), 36-Item Short Form Survey Instrument (SF-36), European Organization for Research and Treatment of Cancer (EORTC-QLQC-30) and complementary module for BC, Functional Assessment of Cancer Therapy - Breast (FACT-B), and the World Health Organization Quality of Life (WHOQOL-bref).

Methodological quality and strength of evidence

The evaluation of the quality of the study using the NOS of the five studies is presented in Table 2. All studies showed high methodological quality, with their only weakness being the insufficient follow-up of participants.

Summary of the results

Only two studies reported the HGS deficit as a dichotomous variable, and the prevalence of HGS decrease ranged from 38.3% (Brandini da Silva et al., 2019) to 60.3% (Kaya et al., 2010).

Regarding the association between HGS and HRQoL, the main results of the studies were summarized in table 1. The studies that performed the association between HGS and HRQoL by correlation coefficient were pooled in meta-analysis of correlation (Figure 2). The correlation coefficient between HGS x score total of HRQoL was 0.26 (95% CI: 0.07-0.35). The analysis includes 220 patients and showed heterogeneity ($I^2 = 53\%$; p= 0.12).

Other meta-analysis of correlation were performed for quality of life questionnaire domains which comparable with each other. The correlation coefficient for HGS x

Table 1. Characteristics of the Studies Included in the Systematic Review.

Author	Country/ Year	Sample Size	Age (mean ± SD)	Measurement of outcomes		Association Measure	Main Results
				Handgrip Strength (HGS)	Health-related Quality of Life (HRQoL)		
Brandini et al.	Brazil 2019	300	58,8 ± 9,6	Equipment: Saehan Hydraulic dynamometer HGS calculated from the average of three measurements. The decrease in HGS was considered a difference of 12% of the LA compared to the LNA.	Breast Cancer Treatment Outcome Scale (BCTOS)	ROC Curve Analysis	HGS deficit 38.3% of patients. Association HGS Deficit X BCTOS scores: Functional status (AUC=0.623; p<0.001); Breast specific pain (AUC =0.596; p=0.005); Edema (AUC=0.583; p=0.013)
Büyükakincak et al.	Turkey 2014	93	47,5 ± 8,8	Equipment: Jamar hydraulic dynamometer. HGS calculated from the average of three measurements in both hands of the patient. Patient with forearm in neutral position and elbow flexed 90°.	36-Item Short Form Survey Instrument (SF-36)	Correlation Analysis	"The HGS values of the participants were not informed. HGS X HRQoL Association: Correlation HGS in the Functional capacity domain r=0.245 p<0.05 Physical aspects domain r=0.227 p<0.05"
Esteban-Simón et al.	Spain 2021	60	52,3± 9,0	Equipment: Digital dynamometer (TKK 5401 Grip-D) . HGS calculated as the best result of two trials on each side. It used absolute HGS and relative HGS (absolute HGS/IMC). It did not specify the measures of decrease of HGS.	European Organization for Research and Treatment of Cancer (EORTC-QLQC-30 and complementary module for breast cancer.	Correlation Analysis	"HGS X HRQoL Association: Absolute HGS: BR23 - arm symptoms/discomfort (r=-0.346; p=0.008) Relative HGS EORTC-QLQC-30 global health status/quality of life (r=0.387; p=0.003); physical function (r=0.254; p= 0.054); fatigue (r=-0.274; p=0.038); BR23 - arm symptoms/discomfort (r=-0.332; p=0.011) "
Kaya et al.	Turkey 2010	67	53,7 ± 12,3	"Equipment: Dynamometer - brand and protocol not specified. HGS calculated from the average of three trials for each side. HGS decrease criterion: 10% difference of LA compared to LNA."	Functional Assessment of Cancer Therapy - Breast (FACT-B)	Multivariate Regression Analysis	"Deficit of HGS = 60.3%. Deficit of HGS = 60.3% HGS X HRQoL Association: Physical well-being (B=-3.20; r2 =0.093 p=0.012 (Multivariate Regression). "
Koca et al.	Turkey 2020	67	50,4 ± 11,2	"Equipment: Jamar hydraulic dynamometer. Equipment: Jamar hydraulic dynamometer. HGS calculated as the average of three measurements obtained according to the recommendations of the American Society of Hand Therapy with a 20-second rest between measurements."	World Health Organization Quality of Life (WHOQOL-bref)	Correlation analysis	HGS X HRQoL Association: General health score: LD (r=0.370; p=0.006)/LE (r=0.414; p=0.002); Physical health score: LD (r=0.465; p≤0.001)/LE (r=0.379; p=0.005); Social health score: LD (r= 0.352; p= 0.011)/LE (r=0.300; p=0.003); Environmental score: LD (r=0.438; p= 0.001)/LE/ r=0.459; p=0.001); Total WHOQOL score: LD/ r=0.406; p=0.003)/LE (r=0.356; p=0.01)

HGS, manual grip strength; HRQoL, quality of life; LD, right side; LE, left side; SD , Standard deviation; LA, affected side; LNA, non-affected side; AUC, area under ROC curve

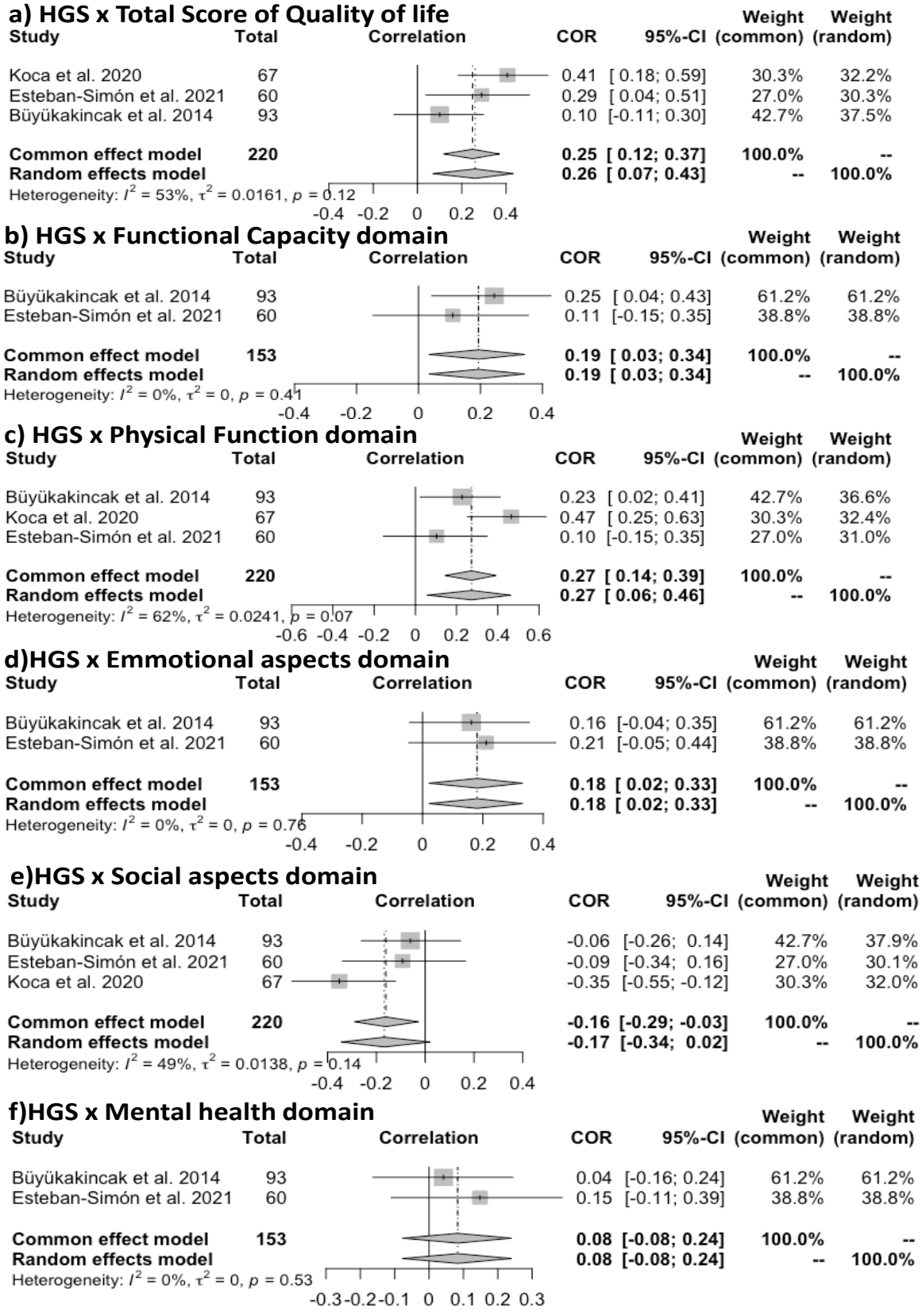

Figure 2. Forest Plots of the Correlation between HGS and HRQoL

functional capacity was 0.19 (95% CI: 0.03-0.34); and between HGS x emotional aspects was 0.18 (95% CI: 0.02-0.33). For this analysis was not verified heterogeneity ($I^2 = 0$). All analysis and data are shown in Figure 2.

Publication bias

Funnel Plot asymmetry was observed in the studies of correlation between HGS and HRQoL, total scores and domains. (Figure 3). Egger test was not performed because

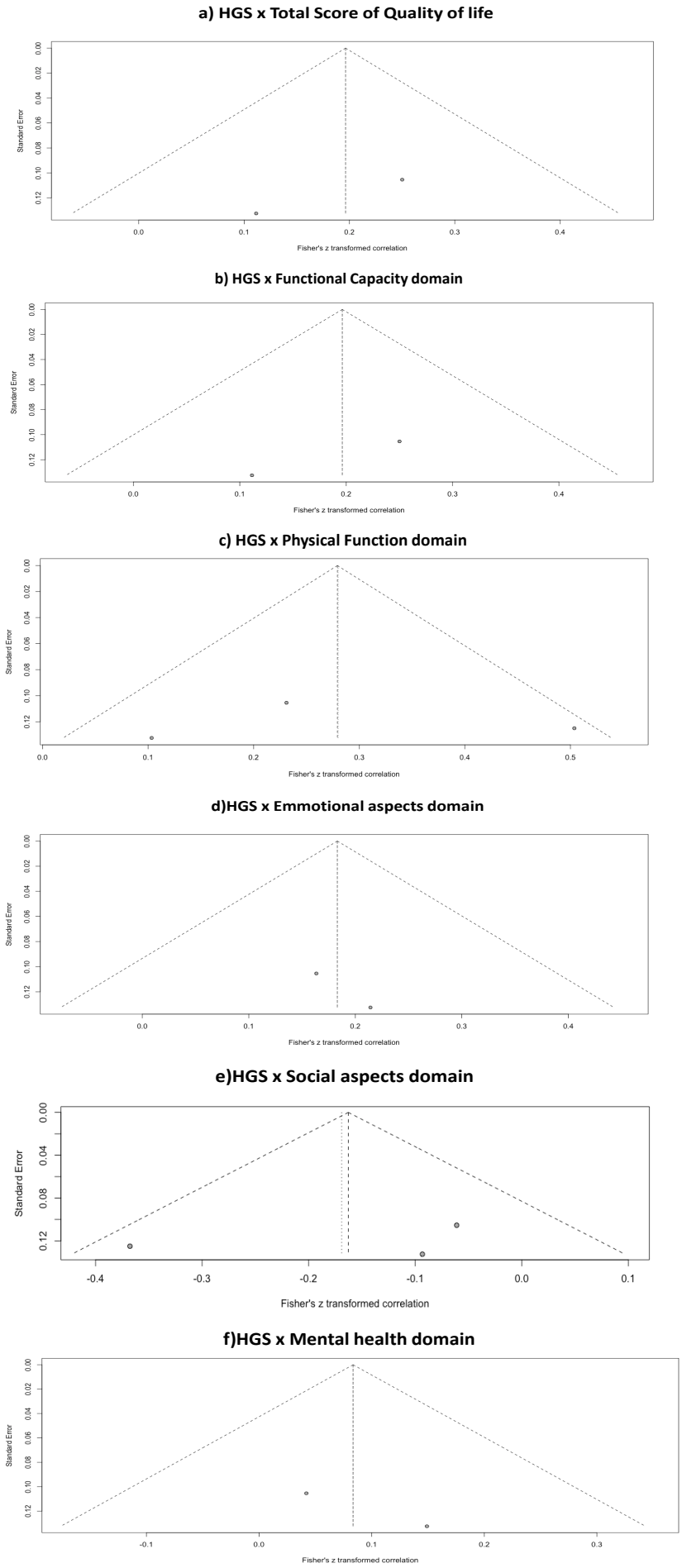

Figure 3. Funnel Plots of the Correlation between HGS and HRQoL

Table 2. Quality Methodological Assessment of Included Studies by the Newcastle-Ottawa Scale

Study	Selection				Comparability	Outcome			Total
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow up of cohorts?	
Brandini et al.	*	*	*	*	*	*	*	*	8
Büyükakinca et al.	*	*	*	*	*	*	-	*	7
Esteban-Simón et al.	*	*	*	*	*	*	*	*	8
Kaya et al.	*	*	*	*	*	*	-	*	7
Koca et al.	*	*	*	*	*	*	-	*	7

*, The study met the criteria.

the number of studies by analysis was insufficient and did not attends the requirements of the test.

Discussion

This systematic review including studies of high methodological quality showed that handgrip strength has a predictive value for HRQoL scores in women who survived BC. To the best of our knowledge, this is the first article that systematically reviewed evidence regarding this association. Our findings add to the body of evidence that advocates the importance of measuring HGS in clinical practice and rehabilitation protocols for BC patients.

The HGS is a measure of physical function, and plays an important general predictive role for muscle mass and strength.(Paek and Choi, 2019a) In patients with BC, HGS deficits have been associated with lower functional capacity; greater fatigue (Cantarero-Villanueva et al., 2012) shoulder deficits, and kinesiophobia (Koca et al., 2020; Lee et al., 2015); and fewer complications from cancer treatments and hospitalizations (Paek and Choi, 2019a).

As a secondary outcome of this review, two papers presents to a high prevalence of women with decreased HGS on the same side to the surgical site, rates ranged 38% to 60%). This not only indicates the loss of muscle function, but also serves as a sign for several other issues that include activities and social participation, such as work and leisure (Annunziata et al., 2018; Schmidt et al., 2018). This is because muscle strength is a predictor of several clinical indicators and basic function required by these women for several daily activities.

Besides that, breast cancer survivors are often overweight. These conditions are related to changes in body composition characterized by fat mass gain and lean mass loss. Consequently, it occurs reduced muscle mass and muscle strength and increased fatigue. In addition, cancer treatments such as chemotherapy contribute to structural and biochemical changes in muscle tissue (Guigni et al., 2018). The combination of these factors contributes to the reduction of HGS. Additionally, the study by Baklaci and Cols (2020) showed that the presence of initial or advanced grade lymphedema is related to lower handgrip strength, possibly due to patients avoiding using the affected arm in usual activities, and this situation usually results in muscle atrophy, weakness, and functional restrictions. The use of multimodal therapies (surgery, radiotherapy, and systemic chemotherapeutic agents) may increase the loss of HGS.

Besides that, it should also be noted that this loss of muscle strength may be related to the late effects of other treatments performed (chemotherapy, radiotherapy, targeted therapy and hormone therapy) (Guigni et al., 2018; Klassen et al., 2017) or resultant complications, such as lymphedema, adhesive capsulitis, pain, and musculoskeletal dysfunction of the shoulder (Cantarero-Villanueva et al., 2012; Esteban-Simón et al., 2021; Kaya et al., 2010; Paek and Choi, 2019a).

There is evidence that HGS in women breast cancer survivors is positively associated with various aspects of physical function, given that better HGS levels favor mobility and performance in usual and self-care activities (Paek and Choi, 2019a). This probably reflects on the quality of life, since the HGS was associated with several dimensions of quality of life, assessed through different instruments, the relationship with dimensions referring to physical function is evident. Furthermore, the association with other dimensions, such as arm symptoms/discomfort and psychosocial factors, suggests a multidimensional relationship between HGS and quality of life in this population.

Based on cross-sectional studies it was possible to verify that HGS is predictor of HRQoL. A detailed analysis of the correlations or verification of these associations showed that the HGS has a convergence with the domains of the WHOQOL-bref questionnaire, with all the domains of the BCTOS, except for the Aesthetic Status subscale; with the scores of functional capacity and physical aspects from SF-36; with the domain of physical well-being of FACT-B; and global health status/QoL, physical function, task performance, fatigue, loss of appetite and arm symptoms/discomfort domains of EORTC-QLQC-30. Meta-analysis confirms the correlation between HGS and total score of HRQoL, functional capacity and emotional aspects. However, the effects was need interpreted with

caution because included only three studies that reported the correlation coefficient and these analyses disregard potential confounding factors.

Previously evidence points that HRQoL is a multidimensional construct directly influenced by issues related to pain (Paek and Choi, 2019a), presence of lymphedema, and associated muscle weakness (De Groef et al., 2016; Lee et al., 2015), and treatments and complications resulting in psychological (Sato et al., 2018) and cognitive issues (Baert et al., 2017). Then, these factors may act as confounding factors and need to be included in a more robust analysis. Two studies, not included in meta-analysis, adjust the association's measures with control of confounding variables and in these studies, HGS remained a predictive variable for HRQoL scores (Brandini da Silva et al., 2019; Kaya et al., 2010).

As a fast, objective, and low-cost measurement parameter, HGS is a useful tool that can be utilized in the routine evaluation of women with BC. Adjustments in the HGS calculation have been proposed in the literature to reduce biases and increase clinical relevance. The relative HGS is a representative indicator of muscle strength, independent of the influence of body mass (Hao et al., 2020), and is taken by adjusting the value measured in HGS by the BMI (Lawman et al., 2016). In the study of (Esteban-Simón et al., 2021) which comparatively analyzed the associations of HGS and relative HGS, the adjusted calculation of relative HGS had a greater association with the HRQoL scores of women with BC, thus corroborating available evidence from other populations (Hao et al., 2020; Lawman et al., 2016).

Limitations

The limitations of this study include the diversity of questionnaires used to evaluate HRQoL and different association measures reported, which limited the generalization and power of meta-analysis performed. The poor description of the protocols to evaluate the HGS in the primary studies made it difficult to compare the procedural questions between the studies.

In conclusion, there is evidence that handgrip strength is correlated to HRQoL scores in female BC survivors. Furthermore, it is observed that cancer-related treatments are associated with decreased handgrip strength and, in turn, a decreased HRQoL in these patients. Since measuring handgrip strength has high clinical value is recommended as part of the evaluation of female cancer survivors to detect damage to muscle function and track adverse health outcomes. The HGS is a low cost measure and useful in different contexts, primary health care, offices and hospitals, its use. However, these findings need to be supported by more evidence.

Author Contribution Statement

ACCS: Protocol/project development; Data collection or management; Data Analysis; Manuscript writing/editing; Approval final version of manuscript.

AB: Data Analysis; Manuscript writing/editing; Approval final version of manuscript.

CMA: Data Analysis; Manuscript writing/editing; Approval final version of manuscript.

AKSM: Data Analysis; Manuscript writing/editing; Approval final version of manuscript.

AST: Protocol/project development; Manuscript writing/editing; Approval final version of manuscript.

DD: Protocol/project development; Data collection or management; Data Analysis; Manuscript writing/editing; Approval final version of manuscript.

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Data Availability Statement

This manuscript use data previously published by other authors and all data are presented into results section.

Conflict of Interest Statement for all authors

The authors have no relevant financial or non-financial interests to disclose.

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