The Cervantes Scale for Measuring Health-Related Quality of Life in Postmenopausal Breast Cancer Survivors During Adjuvant Endocrine Therapy

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Research

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Abstract

Background: Potentially, instruments to manage adverse effects may improve adherence and persistence of treatment, health-related quality of life (HRQL) and breast cancer (BC) outcomes. In this sense, we consider the Cervantes Scale an appropriate option to assess HRQL in BC survivors undergoing adjuvant endocrine therapy with Aromatase Inhibitors (AI), as it is a specific HRQL questionnaire that considers particularities of the perimenopausal and postmenopausal women. The purpose of this study was to analyze the psychometric properties of the 31-item Cervantes Scale (CS-31), 16-item Cervantes Short-Form Scale (CS-16) and 10-item Cervantes Scale (CS-10) and to promote the additional validation for breast cancer (BC) survivors during adjuvant endocrine therapy.

Methods: This prospective study included 89 postmenopausal BC survivors in endocrine therapy. The women completed the CS, Functional Assessment of Chronic Illness Therapy - fatigue (FACIT-F) and Hospital Anxiety and Depression Scale (HADS). The internal consistency, convergent validity, responsiveness analyses and known-group validity of CS were evaluated. Also, simple linear regression assessed the predictive capacity of the CS in relation to the FACIT-F.

Results: The internal consistency was good (Cronbach's alpha: CS-10=0.76; CS-16=0.80; CS-31=0.89). For convergent validity, in general, we identified negative and strong correlations (r>0.6) with exception of moderate correlation between Social/Family Well-Being of FACIT-F and Sexual (r=-0.453) and Couple (r=-0.436) of CS-31, and weak correlation between Social/Family Well-Being of FACIT-F and Sexual (r=-0.289) and Couple (r=-0.287) of CS-16. A prospective improvement in health-related quality of life (HRQL) were identified, except for domains Sexual and Couple of CS-16/CS-31, as well as FACT-G, Social/Family and Functional Well-Being of FACIT-F. The CSs were able to predict changes in the FACIT-F. Furthermore, women with anxiety and depression by HADS presented worse HRQL by CS (p<0.001).

Conclusions: We identified that the CS, highlighting the CS-31, proved to be appropriate for use in routine medical oncology with BC survivors during adjuvant endocrine therapy, although larger studies are needed to confirm these results.

1. Background

Breast cancer (BC) is a heterogeneous disease comprised by several subtypes; hormone receptor-positive (HR+) BC represents 80% of those diagnosed after menopause [1].

Currently, the adjuvant treatment of postmenopausal early-stage HR+ BC with an Aromatase Inhibitor (AI) is considered standard of care [2], being an important ally in increasing of disease-free survival [3]. However, it often causes adverse effects related to the central nervous system such as fatigue, depression and vasomotor symptoms (hot flashes and night sweats); musculoskeletal symptoms as arthralgia and osteoporosis; cardiovascular as hypercholesterolemia and angina; and vulvovaginal symptoms including dryness and dyspareunia [4]. Some of these symptoms are frequent in old age, such as depression [5], or during menopause, with emphasis on vasomotor symptoms [6]. Specifically, in relation to AI, the toxicity can be explained, at least in part, to estrogen depletion [7], hormone that participates in multiple systems and, therefore, has a potential for generalized toxicity in its deprivation [4].

Adverse effects, arising from or exacerbated by AI use, are negatively associated with adherence and persistence of treatment [8] and health-related quality of life (HRQL) [4]. In this sense, the Cervantes Scale (CS) is a HRQL questionnaire that considers particularities of the perimenopausal and postmenopausal women [9] and may be an appropriate option to assess HRQL in BC survivors in AI use.

The CS is a measurement of patients' perception of their own health status or HRQL, i.e. an instrument capable of measuring patient-reported outcome (PRO) [10]. PRO instrument has higher potential to identify adverse effects of therapy (toxicity monitoring); targets for intervention (symptom control); and allow to understand how treatment effectiveness can be affected by patient perceptions about toxicity (adherence to treatment) [11].
Thus, the aim of this study was to analyze the psychometric properties of the 31-item Cervantes Scale (CS-31), 16-item Cervantes Short-Form Scale (CS-16) and 10-item Cervantes Scale (CS-10) and to promote the additional validation of these scales for BC survivors during adjuvant endocrine therapy. To the best of our knowledge, this study is the first one that used the CS to assess HRQL in BC women, especially during AI use.

2. Methods

2.1. Ethics statement, Study design, selection of participants and eligibility criteria

This prospective study was approved by the Human Research Ethics Committee of Federal University of Uberlandia (nº. 1.331.949/15, addendum nº. 2.905.835/18) and complies with the Declaration of Helsinki. All participants signed a free and informed consent.

The study was carried out from January 2016 to August 2018 with postmenopausal BC survivors undergoing adjuvant endocrine therapy with AI at the Clinical Hospital of the Federal University of Uberlandia, Minas Gerais, Brazil. The follow-up time was 24 months, and the face-to-face assessments were performed at three time points: T0, initial follow-up period; T1, intermediate follow-up period, 12 months after T0; and T2, final follow-up period, 24 months after T0, with interviews carried out by properly trained nutritionists.

The recruitment, exclusion criteria and the Cervantes' sample are described in Fig. 1. Clinical and sociodemographic data were obtained through the analysis of medical records or interviews.

2.2. Sample Size

The survivors were recruited at any time of the AI treatment, through the non-probabilistic sampling for convenience. The volunteers were accrued consecutively to avoid selection bias.

The sample size of a group of individuals and three measurements was calculated with the G*Power software, version 3.1 (Düsseldorf, Germany) [12]. An F test was conducted using ANOVA repeated measures, based on an effect size f of 0.25, an alpha level of 0.05 and at 80% power, being required a total of 28 women at each time.

2.3. Cervantes Scale

All participants replied by interview to the CS. Figure 2 provides the items contained in the three versions of the CS.

The CS-31 was developed in 2004 [9] and validated in Brazil in 2012 [13], with Cronbach's alpha for the global score of 0.91 and 0.83, respectively. The CS-31 consists of 31 items rated on a Likert scale from 0 to 5 and divided into four domains, namely Menopause and Health (subdivided into Vasomotor Symptoms, Health and Aging), Sexual, Couple and Psychic, with scores ranging from 0 to 155 points. As recommended, the questionnaires were considered invalid if three or more questions were left unanswered. But, if one or two unanswered questions, the score was obtained by multiplying by a correction factor [9].

In 2013, the CS-31 was reduced to a short 10 item version (CS-10), with Cronbach's alpha of 0.78. The sum of scores of the 10 items provides a global score which can range from 0 to 50 points [14].

In 2015, a 16-item short version (CS-16) was developed as of CS-31, with Cronbach's alpha for the global score of 0.82. This scale maintained the original structure with four domains and the psychometric properties, but was established a rescaling of correction method to convert the original scores into a 0–100 scale [15, 16]. The CS-16 can be administered faster, 2.5 minutes compared to the average application time of 7 minutes of CS-31. Three or more items without answer invalided the questionnaires.
Only CS-31 was validated in Brazil, however, both CS-10 and CS-16 were developed from CS-31, including only issues already present in it. In all the CS, a higher score represents a worse HRQL.

2.3. Psychometric evaluation

All participants replied by interview to the Functional Assessment of Chronic Illness Therapy - fatigue (FACIT-F) and Hospital Anxiety and Depression Scale (HADS), which are validated instruments and already well established for BC patients.

Validation Instruments.

FACIT-F (version 4). This scale of 40-item includes the 27-item Functional Assessment of Cancer Therapy-General (FACT-G) that assess the HRQL and 13 items that assess self-reported fatigue [17]. This instrument measures four well-being subscales (physical, social/family, emotional and functional), one fatigue subscale, and derives to calculate the FACIT-F Trial Outcome Index (TOI) (score range 0-108), the FACT-G total score (score range 0-108) and the FACIT-F total score (score range 0-160). Items are rated on a Likert scale from 0 (not at all) to 4 (very much). A higher score represents a better HRQL. The FACIT-F has been previously validated in Brazil [18]. In the present study, the Cronbach's alpha were FACIT-F $\alpha = 0.93$ (95% confidence interval [CI] = 0.90–0.95), FACIT-F TOI $\alpha = 0.93$ (95% [CI] = 0.90–0.95) and FACT-G $\alpha = 0.87$ (95% [CI] = 0.82–0.90).

HADS. This self-reported questionnaire comprising seven items target anxiety (subscale HADS-A) and seven items target depression (subscale HADS-D) [19]. Items are rated using a 4-point Likert-type scale with scores of 0 (minimally present) to 3 (maximally present). The scores range for HADS-A and HADS-D from 0 to 21, with higher scores indicating greater distress. We adopted the following cut-off for both scales: <8 for non-cases, ≥ 8 for doubtful cases and ≥ 11 for the identification of cases [19]. The HADS has been previously validated in Brazil [20]. In this study, the Cronbach's alpha were HADS-A $\alpha = 0.76$ (95% [CI] = 0.67–0.83) and HADS-D $\alpha = 0.80$ (95% [CI] = 0.72–0.85).

2.4. Statistical Analysis

Internal consistency was studied considering the global score, including all items, and for each domain. We use Cronbach’s alpha coefficient, considering adequate values between 0.70 and 0.95 [21].

Convergent analyses were assessed by determining the correlation between the CS (global score and domains) and a specific related measure from FACIT-F. We hypothesized that global score between CS and FACIT-F, as they are general measures, as well as constructs indirectly related (Sexual and Couple of CS with Social/Family Well-Being of FACIT-F) should correlate with $r > 0.4$. Regarding that similar constructs, as Psychic of CS and Emotional Well-Being of FACIT-F, our hypothesis was correlations with $r > 0.6$. Correlation coefficients < 0.4 were considered weak correlations, between 0.4 and 0.6, moderate correlations, and > 0.6, strong correlations [22].

For the responsiveness analyses, we assessed the change in global and domains scores of FACIT-F and CS between the three time points (T0, T1 and T2). Differences were evaluated using One-way ANOVA test with repeated measures and Sidak post-hoc, or the non-parametric Friedman with multiple comparison tests.

Simple linear regression was performed to verify the predictive capacity of the CS Global in relation to the FACIT-F Total score, FACIT-F TOI and FACT-G.

The known-group validation analysis was performed to assess if the instrument would be able to discriminate between subgroups of women, using one-way ANOVA with Sidak post-hoc. The CS global scores were compared between non-cases, doubtful cases and cases of anxiety and depression by HADS. We hypothesized that those women with higher scores for both anxiety and depression, would have a worse HQRL. In BC patients, the HRQL is closely related with these psychological disorders [23].

All statistical analyzes were performed using IBM SPSS Statistics (Chicago, IL, USA), software package (SPSS Statistics for Windows, version 21.0), considering statistically significant p-values of less than 0.05.
3. Results

Table 1 shows the demographic and clinical characteristics of the 89 BC survivors.

The median (p25-p75) of age was 65 (58.5–69.5) years, the median of time using AI was 29.5 (18.1–41.8) months, of time diagnosis was 4 (2–5) years, and of climacteric period was 16 (8–20) years. Most women were not married (56.2%, n = 50), but the most have partner (75.3%, n = 67). Regarding adjuvant endocrine therapy, 44.9% (n = 40) of women used tamoxifen prior to starting AI.
Table 1
Demographic and clinical characteristics of the breast cancer survivors during endocrine therapy.

| Characteristics                          | Overall (n = 89) |
|-----------------------------------------|-----------------|
| Age (years)                             | 65 (58.5−69.5)  |
| < 60                                    | 25 (28.1)       |
| ≥ 60                                    | 64 (71.9)       |
| **Marital Status**                      |                 |
| Single/ Divorced/Separated/Widow        | 50 (56.2)       |
| Married                                 | 39 (43.8)       |
| **Partner**                             |                 |
| No                                      | 22 (24.7)       |
| Yes                                     | 67 (75.3)       |
| **Educational Level**                   |                 |
| Below high school                      | 61 (68.5)       |
| High school or higher education         | 28 (31.5)       |
| **Income (minimum wage)**               |                 |
| < 3                                     | 53 (59.6)       |
| ≥ 3                                     | 36 (40.4)       |
| **Work activity**                       |                 |
| Active                                  | 22 (24.7)       |
| Inactive                                | 67 (75.3)       |
| **Surgery**                             |                 |
| Breast-conserving surgery               | 51 (57.3)       |
| Mastectomy                              | 38 (42.7)       |
| **Prior Radiotherapy**                  |                 |
| No                                      | 14 (15.7)       |
| Yes                                     | 75 (84.3)       |
| **Prior Chemotherapy**                  |                 |
| No                                      | 21 (23.6)       |
| Yes                                     | 68 (76.4)       |
| **Chemotherapy Regimen**                |                 |
| Adjuvant                                | 53 (77.9)       |
| Neoadjuvant                             | 15 (22.1)       |
| **Prior Tamoxifen**                     |                 |
| No                                      | 49 (55.1)       |
| Characteristics                      | Overall (n = 89) |
|-------------------------------------|-----------------|
| Yes                                 | 40 (44.9)       |

**Tumoral Subtype**

|                      |        |
|----------------------|--------|
| Ductal               | 86 (96.6) |
| Lobular              | 3 (3.4)  |

**Clinical Stage**

|                      |        |
|----------------------|--------|
| I                    | 26 (29.2) |
| II                   | 48 (53.9) |
| III                  | 13 (14.6) |
| NR                   | 2 (2.2)  |

**Tumor Grade**

|                      |        |
|----------------------|--------|
| G1                   | 14 (15.7) |
| G2                   | 66 (74.2) |
| G3                   | 5 (5.6)   |
| NR                   | 4 (4.5)   |

**Molecular Subtype**

|                                          |        |
|-----------------------------------------|--------|
| ER + and/or PR+, HER2- and Ki-67 < 14% | 17 (19.1) |
| ER + and/or PR+, HER2- and Ki-67 ≥ 14% | 37 (41.6) |
| ER + and/or PR+, HER2+                  | 29 (32.6) |
| NR                                      | 6 (6.7)   |

**Months since start on AI**

|                          |        |
|--------------------------|--------|
|                          | 29.5 (18.1–41.8) |

**Years since diagnosis**

|                      |        |
|----------------------|--------|
|                      | 4 (2–5)  |

**Years since last menstrual period**

|                      |        |
|----------------------|--------|
|                      | 16 (8–20) |

Continuous variables are shown as median (p25-p75), and categorical variables are shown as absolute numbers and percentage frequency (in parentheses); Time point: T0, Initial follow-up period; Prior, before starting AI use; AI, aromatase inhibitor; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor type 2 receptor; Ki-67, Ki-67 antigen; -, negative; +, positive; NR: Not reported; G1: Well-differentiated tumor (low grade); G2: Moderately differentiated tumor (intermediate grade); G3: Poorly differentiated tumor (high grade). The Brazilian minimum wage was R$ 880.00.

**Internal consistency:** All CS presented good global internal consistency (Cronbach’s alpha: CS-10 = 0.76; CS-16 = 0.80 and CS-31 = 0.89), without significantly change if single item deleted (Tables 2–4). As for the domains, Psychic, Sexual and Couple of CS-16 did not present adequate Cronbach’s alpha coefficient, i. e. values between 0.70 and 0.95 [21], indicating low internal reliability (Table 3).
Table 2
Cronbach’s α of the 10-item Cervantes Scale (CS-10).

| Item | Descriptors                                                                 | Mean (SD)  | Cronbach’s α if Item Deleted |
|------|-----------------------------------------------------------------------------|------------|------------------------------|
| 4    | Aching in muscles and/or joints                                            | 3.38 (1.39) | 0.744                       |
| 8    | I am afraid of performing physical efforts because my urine leaks           | 0.97 (1.66) | 0.755                       |
| 5    | I feel tired since I get up                                                 | 2.07 (1.94) | 0.702                       |
| 7    | I feel anxious or nervous                                                  | 2.34 (1.91) | 0.723                       |
| 6    | I have the perception of being useless                                      | 1.33 (1.76) | 0.729                       |
| 2    | I feel my heart beating quickly and out of control                          | 1.80 (1.77) | 0.732                       |
| 9    | I have vaginal discomfort and dryness                                      | 1.71 (1.95) | 0.757                       |
| 1    | I have hot flushes                                                         | 2.42 (2.01) | 0.735                       |
| 10   | I have noticed skin dryness                                                | 3.37 (1.89) | 0.762                       |
| 3    | I cannot get sufficient sleep                                               | 3.06 (1.78) | 0.749                       |

Cronbach’s α (95% [CI]) ¹

0.76 (95% [CI] = 0.68–0.83)

Time point: T0, Initial follow-up period; SD, Standard deviation; CI: Confidence interval. ¹No single item significantly modified the internal consistency of the CS-10 when deleted.
Table 3
Cronbach’s α of the 16-item Cervantes Short-Form Scale (CS-16).

| Domain                         | Cronbach’s α (95% CI) | Item | Descriptors                                                                 | Mean (SD) | Cronbach’s α if Item Deleted |
|--------------------------------|------------------------|------|------------------------------------------------------------------------------|-----------|-----------------------------|
| Menopause and Health (n = 89)  | 0.73 (0.64–0.81)       | 3    | During the day, I feel my head hurts more and more                           | 1.38 (1.54)| 0.713                       |
|                                |                        | 4    | Even I sleep, I cannot rest                                                  | 2.72 (1.91)| 0.685                       |
|                                |                        | 7    | I am afraid of performing physical efforts because my urine leaks            | 0.97 (1.65)| 0.729                       |
|                                |                        | 5    | I feel my heart beating quickly and out of control                           | 1.80 (1.77)| 0.705                       |
|                                |                        | 8    | My health causes me problems with housework                                  | 2.32 (1.95)| 0.697                       |
|                                |                        | 2    | I have hot flushes                                                           | 2.42 (2.01)| 0.699                       |
|                                |                        | 9    | I have noticed skin dryness                                                  | 3.37 (1.89)| 0.745                       |
|                                |                        | 6    | I feel tingling in my hands and feet                                         | 2.19 (1.90)| 0.686                       |
|                                |                        | 1    | Suddenly, I start sweating without effort                                    | 2.72 (2.02)| 0.717                       |
| Psychic (n = 89)               | 0.69 (0.56–0.79)       | 12   | I feel tired since I get up                                                   | 2.07 (1.94)| 0.630                       |
|                                |                        | 10   | I feel anxious or nervous                                                    | 2.34 (1.91)| 0.546                       |
|                                |                        | 11   | Everything bothers me, including the things that used to amuse me            | 1.76 (1.76)| 0.610                       |
| Sexual (n = 86)                | 0.67 (0.50–0.78)       | 13   | I am satisfied with my sexual intercourse                                    | 1.71 (2.10)| -                           |
|                                |                        | 14   | In my life, sex is                                                           | 1.58 (1.95)| -                           |
| Couple (n = 67)                | 0.59 (0.34–0.75)       | 15   | I consider myself happy in my relationship                                   | 2.97 (1.91)| -                           |
|                                |                        | 16   | My role as wife or partner is                                                | 3.49 (1.86)| -                           |
| Global Score ¹                 | 0.80 (0.71–0.86)       |      |                                                                              |           |                             |

Time point: T0, Initial follow-up period; SD, Standard deviation; CI: Confidence interval. ¹No single item significantly modified the internal consistency of the CS-16 global and domains when deleted.
Table 4
Cronbach's α of the 31-item Cervantes Scale (CS-31).

| Domain                  | Cronbach's α (95% [CI]) | Item | Descriptors                                                                 | Mean (SD)     | Cronbach's α if Item Deleted |
|------------------------|--------------------------|------|------------------------------------------------------------------------------|---------------|-----------------------------|
| Menopause and Health   | 0.81 (0.75–0.86)         | 1    | During the day, I feel my head hurts more and more                           | 1.38 (1.54)   | 0.799                       |
| (n = 89)               |                          | 11   | Even I sleep, I cannot rest                                                 | 2.72 (1.91)   | 0.786                       |
|                        |                          | 14   | I believe I'm retaining fluid, because I'm swollen                           | 1.98 (1.90)   | 0.800                       |
|                        |                          | 16   | Aching in muscles and/or joints                                             | 3.38 (1.39)   | 0.798                       |
|                        |                          | 18   | I am afraid of performing physical efforts because my urine leaks           | 0.97 (1.66)   | 0.805                       |
|                        |                          | 23   | I feel my heart beating quickly and out of control                          | 1.80 (1.77)   | 0.795                       |
|                        |                          | 25   | My health causes me problems with housework                                  | 2.31 (1.95)   | 0.787                       |
|                        |                          | 27   | I have vaginal discomfort and dryness                                       | 1.71 (1.95)   | 0.806                       |
|                        |                          | 29   | I have hot flushes                                                          | 2.42 (2.01)   | 0.789                       |
|                        |                          | 3    | Suddenly, I feel very warm                                                  | 2.84 (1.89)   | 0.798                       |
|                        |                          | 31   | I have noticed skin dryness                                                 | 3.37 (1.89)   | 0.813                       |
|                        |                          | 5    | I cannot get sufficient sleep                                                | 3.06 (1.78)   | 0.797                       |
|                        |                          | 7    | I feel tingling in my hands and feet                                        | 2.19 (1.90)   | 0.789                       |
|                        |                          | 9    | Suddenly, I start sweating without effort                                   | 2.72 (2.02)   | 0.797                       |
|                        |                          | -20  | I'm as healthy as anyone my age                                              | 1.53 (1.52)   | 0.800                       |
| Psychic                | 0.85 (0.80–0.90)         | 2    | I feel anxious or nervous                                                   | 2.34 (1.91)   | 0.831                       |
| (n = 89)               |                          | 6    | Everything bothers me, including the things that used to amuse me           | 1.76 (1.77)   | 0.839                       |
|                        |                          | 10   | I lost the ability to relax                                                  | 2.24 (1.90)   | 0.836                       |
|                        |                          | 12   | I feel like the world is spinning around me                                 | 1.91 (1.92)   | 0.852                       |
|                        |                          | 17   | I believe people are better without me                                       | 0.70 (1.46)   | 0.847                       |
|                        |                          | 19   | I feel tired since I get up                                                  | 2.07 (1.94)   | 0.834                       |
| Domain     | Cronbach’s α (95% [CI]) | Item | Descriptors                                      | Mean (SD)  | Cronbach’s α if Item Deleted |
|------------|--------------------------|------|-------------------------------------------------|------------|-----------------------------|
|            |                          | 21   | I have the perception of being useless          | 1.33 (1.76) | 0.825                       |
|            |                          | 24   | Sometimes I think I don’t care if I was dead   | 1.06 (1.73) | 0.847                       |
|            |                          | 28   | I feel empty                                    | 2.06 (1.99) | 0.824                       |
| Sexual     | 0.84 (0.76–0.88)         | 4    | My interest in sex keeps the same as always     | 1.07 (1.65) | 0.768                       |
| (n = 89)   |                          | 30   | In my life, sex is                              | 1.58 (1.95) | 0.785                       |
|            |                          | 22   | I’m having sexual intercourse as often as before| 0.69 (1.37) | 0.776                       |
|            |                          | 15   | I am satisfied with my sexual intercourse       | 1.71 (2.10) | 0.812                       |
|            |                          | 8    | I consider myself happy in my relationship     | 2.97 (1.92) | 0.619                       |
| Couple     | 0.75 (0.63–0.84)         | 26   | In my relationship, I feel that I am treated as an equal | 3.01 (2.02) | 0.592                       |
| (n = 67)   |                          | 13   | My role as wife or partner is                   | 3.49 (1.86) | 0.782                       |
| Global Score | 0.89 (0.84–0.92) |      |                                                  |            |                             |

Time point: T0, Initial follow-up period; SD, Standard deviation; CI: Confidence interval. ¹No single item significantly modified the internal consistency of the CS-31 global and domains when deleted.

**Convergent analyses.** In general, we identified negative and strong correlations ($r > 0.6$), with the exception of the moderate correlation between Social/Family Well-Being of FACIT-F and Sexual ($r=-0.453; 95\% \text{ CI}=-0.656 — -0.223$) and Couple ($r=-0.436; 95\% \text{ CI}=-0.635 — -0.197$) domains of CS-31, and of the weak correlation between Social/Family Well-Being of FACIT-F and Sexual ($r=-0.289; 95\% \text{ CI}=-0.483 — -0.081$) and Couple ($r=-0.287; 95\% \text{ CI}=-0.494 — -0.068$) domains of CS-16. Thus, only Sexual and Couple of the CS-16 did not reach the expected correlation with FACIT-F (Table 5).
Table 5
Convergent analyses between the CS (global score and domains) and a specific related measure from FACIT-F.

| Cervantes Scale               | FACIT-F |
|-------------------------------|---------|
|                               | Emotional Well-Being (EWB) | Physical Well-Being (PWB) | Functional Well-Being (FWB) | Social/Family Well-Being (SWB) | Fatigue Subscale (FS) | FACIT-F Trial Outcome Index (TOI) | FACIT-F Total Score | FACT-G Total Score |
| CS-10 Global Score            | -0.685$^1$ | -0.685$^1$ | -0.580$^1$ | -0.336$^1$ | -0.664$^1$ | -0.705$^1$ | -0.739$^1$ | -0.721$^1$ |
| ($n = 89$)                    | < 0.001$^4$ | < 0.001$^4$ | < 0.001$^4$ | < 0.001$^3$ | < 0.001$^4$ | < 0.001$^3$ | < 0.001$^4$ | < 0.001$^3$ |
| CS-16 Menopause and Health    | -0.576$^1$ | -0.712$^1$ | -0.592$^1$ | -0.323$^1$ | -0.708$^1$ | -0.764$^1$ | -0.752$^1$ | -0.691$^1$ |
| ($n = 86$)                    | < 0.001$^4$ | < 0.001$^4$ | < 0.001$^4$ | < 0.001$^4$ | < 0.001$^4$ | < 0.001$^4$ | < 0.001$^4$ | < 0.001$^4$ |
| Psychic                       | -0.708$^1$ | -0.630$^1$ | -0.585$^1$ | -0.504$^1$ | -0.672$^1$ | -0.725$^1$ | -0.785$^1$ | -0.788$^1$ |
|                              | < 0.001$^4$ | < 0.001$^4$ | < 0.001$^4$ | < 0.001$^4$ | < 0.001$^4$ | < 0.001$^4$ | < 0.001$^4$ | < 0.001$^4$ |
| Global Score                  | -0.601$^1$ | -0.687$^1$ | -0.594$^1$ | -0.502$^1$ | -0.697$^1$ | -0.748$^1$ | -0.797$^1$ | -0.785$^1$ |
| ($n = 86$)                    | < 0.001$^4$ | < 0.001$^4$ | < 0.001$^4$ | < 0.001$^3$ | < 0.001$^3$ | < 0.001$^3$ | < 0.001$^3$ | < 0.001$^3$ |
| CS-31 Menopause and Health    | -0.674$^1$ | -0.773$^1$ | -0.613$^1$ | -0.234$^1$ | -0.696$^1$ | -0.762$^1$ | -0.755$^1$ | -0.737$^1$ |
| ($n = 68$)                    | < 0.001$^4$ | < 0.001$^4$ | < 0.001$^4$ | < 0.001$^4$ | < 0.001$^3$ | < 0.001$^3$ | < 0.001$^3$ | < 0.001$^3$ |
| Psychic                       | -0.766$^1$ | -0.694$^1$ | -0.560$^1$ | -0.492$^1$ | -0.713$^1$ | -0.737$^1$ | -0.793$^1$ | -0.784$^1$ |
|                              | < 0.001$^4$ | < 0.001$^4$ | < 0.001$^4$ | < 0.001$^4$ | < 0.001$^4$ | < 0.001$^4$ | < 0.001$^4$ | < 0.001$^4$ |
| Sexual                        | -0.112$^1$ | -0.083$^1$ | -0.126$^1$ | -0.453$^1$ | -0.152$^1$ | -0.131$^1$ | -0.231$^1$ | -0.268$^2$ |
|                              | 0.363$^4$ | 0.503$^4$ | 0.304$^4$ | < 0.001$^4$ | 0.215$^4$ | 0.289$^4$ | 0.058$^4$ | 0.027$^4$ |
| Couple                        | -0.154$^1$ | -0.110$^1$ | -0.089$^1$ | -0.436$^1$ | -0.124$^1$ | -0.122$^1$ | -0.231$^1$ | -0.283$^*$$^1$ |
|                              | 0.210$^4$ | 0.371$^4$ | 0.471$^4$ | < 0.001$^4$ | 0.314$^4$ | 0.320$^4$ | 0.058$^4$ | 0.019$^4$ |
| Time point: T0, Initial follow-up period; CS-31: 31-item Cervantes Scale; CS-16: 16-item Cervantes Short-Form Scale; CS-10: 10-item Cervantes Scale; FACIT-F Trial Outcome Index (TOI): PWB + FWB + FS; FACIT-F Total Score: EWB + PWB + FWB + SWB + FS; FACT-G Total Score: EWB + PWB + FWB + SWB.  
1 Correlation is significant at the 0.01 level (2-tailed); 2 Correlation is significant at the 0.05 level (2-tailed). 3 Pearson correlation; 4 Spearman correlation. Bold value is statistically significant at p < 0.05.  

### Responsiveness analyses
In Table 6, we identified that there was a significant improvement in HRQL by the CS Global scores (CS-10, p = 0.004; CS-16, p = 0.001; CS-31, p = 0.001) as well as by the FACIT-F Total Score (p = 0.044), throughout the study. All the significances indicate worse global and domains scores in T0 compared to T1 and T2, either by CS or FACIT-F, indicating that women started endocrine therapy with a worse HRQL. The CS Global score, the Menopause and Health score (CS-16, p < 0.001; CS-31, p = 0.004) and Psychic score (CS-31, p = 0.002) were higher in T0 compared to T1 and T2, and did not differ between T1 and T2. The Psychic score (CS-16, p = 0.011), Emotional Well-Being (p = 0.029), Physical Well-Being (p = 0.016) and FACIT-F TOI (p = 0.017) differed statistically between T0 and T2, with higher scores at baseline. The Fatigue Subscale had higher at T0 when compared to T1 (p = 0.012). The domains Sexual and Couple (CS-16 and CS-31), as well as FACT-G, Functional and Social/Family Well-Being (FACIT-F) did not differ statistically.

#### Table 6: Correlations between Cervantes Scale and FACIT-F

| Cervantes Scale | FACIT-F |
|----------------|---------|
| Emotional Well-Being (EWB) | Physical Well-Being (PWB) | Functional Well-Being (FWB) | Social/Family Well-Being (SWB) | Fatigue Subscale (FS) | FACIT-F Trial Outcome Index (TOI) | FACIT-F Total Score | FACT-G Total Score |
| Global Score | - .728<sup>1</sup> | - .732<sup>1</sup> | - .639<sup>1</sup> | - .507<sup>1</sup> | - .733<sup>1</sup> | - .777<sup>1</sup> | - .837<sup>1</sup> | - .842<sup>1</sup> |
|              | < 0.001<sup>4</sup> | < 0.001<sup>4</sup> | < 0.001<sup>4</sup> | < 0.001<sup>3</sup> | < 0.001<sup>3</sup> | < 0.001<sup>3</sup> | < 0.001<sup>3</sup> | < 0.001<sup>3</sup> |
Table 6
Variation in the domains and global scores of the Cervantes Scale and FACT over time.

| Dependent variables | n  | Score range | Mean ± SD or Median (p25-p75) | \( p \) value |
|---------------------|----|-------------|-------------------------------|--------------|
|                     |    |             | T0                            | T1           | T2           |
| **CS-10**           |    |             |                               |              |
| Global score        | 38 | 0–50        | 22.7 ± 10.2\(^a\)            | 19.4 ± 9.0\(^b\) | 18.9 ± 8.5\(^b\) | 0.004 |
| **CS-16**           |    |             |                               |              |
| Menopause and Health| 27 | 0–45        | 21 (14–31)\(^a\)            | 17 (10–24)\(^b\) | 17 (10–25)\(^b\)  | < 0.001 |
| Psychic             | 27 | 0–15        | 5 (3–11)\(^a\)             | 4 (2–9)\(^a,b\) | 4 (0–8)\(^b\)      | 0.011 |
| Sexual              | 27 | 0–10        | 7 (2–10)                   | 6 (3–8)       | 6 (4–10)        | 0.963 |
| Couple              | 27 | 0–10        | 4 (1–9)                    | 4 (1–10)      | 5 (1–10)        | 0.593 |
| Global Score        | 27 | 0–100       | 61 (52–73)\(^a\)          | 55 (44–63)\(^b\) | 59 (39–67)\(^b\)  | 0.001 |
| **CS-31**           |    |             |                               |              |
| Menopause and Health| 21 | 0–75        | 36 (25.5–49.5)\(^a\)       | 28 (20.5–41.5)\(^b\) | 26 (16.5–42)\(^b\) | 0.004 |
| Psychic             | 21 | 0–45        | 20 (8.5–27.5)\(^a\)       | 9 (4.5–16.5)\(^b\) | 14 (4.22.8)\(^b\)  | 0.002 |
| Sexual              | 21 | 0–20        | 14 (4.5–20)                | 15 (8–18)     | 14 (7–20)        | 0.831 |
| Couple              | 21 | 0–15        | 3 (0.5–6.5)                | 4 (0.5–7.5)   | 6 (0.5–9.5)      | 0.461 |
| Global Score        | 21 | 0–155       | 88 (45.5–94.5)\(^a\)     | 64 (40–76)\(^b\) | 68 (40–87)\(^b\)  | 0.001 |
| **FACIT-F**         |    |             |                               |              |
| Emotional Well-Being (EWB) | 38 | 0–24        | 18 (14–21)\(^a\)          | 18 (15.8–21)\(^a,b\) | 18.5 (16.8–22)\(^b\) | 0.029 |
| Physical Well-Being (PWB) | 38 | 0–28        | 19 (16–23)\(^a\)          | 21 (16–26)\(^a,b\) | 21.5 (18–24)\(^b\)  | 0.016 |
| Functional Well-Being (FWB) | 38 | 0–28        | 18.6 ± 5.2                | 18.5 ± 4.8    | 18.2 ± 4.6       | 0.799 |
| Social/Family Well-Being (SWB) | 38 | 0–28        | 18.4 ± 5.2                | 18.4 ± 5.6    | 17.9 ± 5.1       | 0.702 |
| Fatigue Subscale (FS) | 38 | 0–52        | 35.5 (27-44.3)\(^a\)     | 39.5 (32.8–46.3)\(^b\) | 41.5 (35–45)\(^a,b\) | 0.012 |
| FACIT-F Trial Outcome Index (TOI) | 38 | 0–108       | 73.4 ± 18.1\(^a\)         | 77.4 ± 17.0\(^a,b\) | 78.9 ± 13.6\(^b\)  | 0.017 |
| FACIT-F Total Score  | 38 | 0–160       | 109.5 ± 24.8              | 114.0 ± 22.9  | 115.5 ± 19.3     | 0.044 |
| FACT-G Total Score   | 38 | 0–108       | 73.7 ± 15.5               | 75.5 ± 15.1   | 76.0 ± 13.0      | 0.364 |

Time point: T0, Initial follow-up period; T1, Intermediate period, corresponding to 12 months after T0; and T2, Final follow-up period, corresponding to 24 months after T0; CS-31: 31-item Cervantes Scale; CS-16: 16-item Cervantes Short-Form Scale; CS-10: 10-item Cervantes Scale; FACIT-F Trial Outcome Index (TOI): Physical Well-Being + Functional Well-Being + Fatigue Subscale; FACIT-F Total Score: Emotional Well-Being + Physical Well-Being + Functional Well-Being + Fatigue Subscale; FACT-G Total Score: Emotional Well-Being + Physical Well-Being + Functional Well-Being + Social/Family Well-Being + Fatigue Subscale; FACT-G Total Score: Emotional Well-Being + Physical Well-Being + Functional Well-Being + Social/Family Well-Being.
Well-Being. SD, Standard deviation. One-way ANOVA test with repeated measures and Sidak post-hoc, or the non-parametric Friedman with multiple comparison tests. Bold value is statistically significant at p < 0.05.

**Simple linear regression analyses.** All analyses were statistically significant (p < 0.001). The results indicated that the CS Global scores, especially the CS-31, were able to predict changes in the FACIT-F Total score, FACIT-F TOI and FACT-G Total score (Table 7).

| Table 7 | FACT variance explained by the Cervantes Scale: simple linear regression analysis. |
|---------|--------------------------------------------------------------------------------|
| Independent Variable | Dependent Variable | B   | SE  | 95 % IC  | t   |
| Global Score CS-10 (n = 89) | FACIT-F TOI | -1.229 | 0.133 | -1.493 to -.966 | -9.269 |
|                      | Total Score | -1.670 | 0.163 | -1.994 to -1.346 | -10.243 |
|                      | FACIT-F TOI | -1.038 | 0.107 | -1.251 to -.825 | -9.693 |
| Global Score CS-16 (n = 86) | FACIT-F TOI | -0.930 | 0.090 | -1.109 to -.751 | -10.329 |
|                      | Total Score | -1.280 | 0.106 | -1.491 to -1.070 | -12.092 |
|                      | FACIT-F TOI | -0.799 | 0.069 | -.935 to -.662 | -11.626 |
| Global Score CS-31 (n = 68) | FACIT-F TOI | -0.547 | 0.055 | -0.656 to -.438 | -10.028 |
|                      | Total Score | -0.756 | 0.061 | -0.878 to -.635 | -12.439 |
|                      | FACIT-F TOI | -0.479 | 0.038 | -0.555 to -.404 | -12.662 |

Time point: T0, Initial follow-up period; CS-31: 31-item Cervantes Scale; CS-16: 16-item Cervantes Short-Form Scale; CS-10: 10-item Cervantes Scale. SE, Standard error; CI: Confidence interval; B, unstandardized coefficient; r2, coefficient of determination; t, T-test coefficient; FACIT-F Trial Outcome Index (TOI): Physical Well-Being + Functional Well-Being + Fatigue Subscale; FACIT-F Total Score: Emotional Well-Being + Functional Well-Being + Fatigue Subscale; FACT-G Total Score: Emotional Well-Being + Physical Well-Being + Functional Well-Being + Social/Family Well-Being. All p-values are < 0.001.

**Known-group validity.** As previously hypothesized, those women with higher scores for both anxiety and depression by HADS presented worse HRQL by CS when compared to subgroup non-cases. Regarding the anxiety, the analysis of CS-16 revealed that the subgroup cases had worse HRQL even when compared to the subgroup doubtful cases (Table 8).
Table 8
Known-group validation analyses.

| Cervantes Scale | Mean ± SD                      |
|-----------------|--------------------------------|
|                 | Anxiety (HADS-A)               | Depression (HADS-D)               |
|                 | Non-cases                      | Doubtful cases                   | Cases          |
| Global Score CS-10 | 17.1 ± 8.0<sup>a</sup>     | 24.4 ± 9.4<sup>b</sup>       | 30.2 ± 9.1<sup>b</sup>       | 17.8 ± 8.9<sup>a</sup>     | 27.7 ± 10.0<sup>b</sup> | 28.6 ± 8.0<sup>b</sup>       |
| n               | 43                             | 22                             | 24                         | 50                         | 13                         | 26                         |
| Global Score CS-16 | 48.8 ± 12.3<sup>a</sup>      | 61.2 ± 11.3<sup>b</sup>      | 69.5 ± 9.8<sup>c</sup>      | 50.4 ± 13.2<sup>a</sup>    | 63.4 ± 9.8<sup>b</sup>     | 68.1 ± 10.3<sup>b</sup>      |
| n               | 48                             | 22                             | 23                          | 48                         | 13                         | 25                         |
| Global Score CS-31 | 53.4 ± 20.9<sup>a</sup>      | 80.1 ± 20.3<sup>b</sup>      | 94.7 ± 15.7<sup>b</sup>      | 56.0 ± 23.4<sup>a</sup>    | 85.1 ± 16.4<sup>b</sup>     | 90.6 ± 17.6<sup>b</sup>      |
| n               | 33                             | 17                             | 18                          | 37                         | 10                         | 21                         |

Time point: T0, Initial follow-up period; CS-31: 31-item Cervantes Scale; CS-16: 16-item Cervantes Short-Form Scale; CS-10: 10-item Cervantes Scale. SD, Standard deviation; HADS-A: Hospital Anxiety and Depression Scale, subscale anxiety; HADS-D: Hospital Anxiety and Depression Scale, subscale depression. One-way ANOVA with Sidak post-hoc. All p-values are < 0.001.

4. Discussion

The psychometric properties revealed that CS-31, CS-16 and CS-10 are valid instruments for assessing HRQL in BC survivors during adjuvant endocrine therapy. All the CS presented adequate internal consistency; satisfactory convergent validity for CS global and for almost all domains, except for Sexual and Couple of CS-16; and known-group validity, with statistical significance between anxiety and depression and worse HRQL. Furthermore, we identified a prospective improvement in HRQL of the baseline for the other time points. The CS were able to predict changes in the FACIT-F, especially the CS-31. To the best of our knowledge, our study is the first one that used the CS to assess HRQL in BC women, especially during adjuvant endocrine therapy.

CS-10 contains a small number of items (32% of the original length), is simple to apply and does not include sexual and couple relationship issues, which can often be embarrassing for respondents. However, the items on this scale are not divided into domains, allowing more restricted analyses. The authors of CS-10 constructed this instrument to a quick menopausal symptom assessment, not specifically to assessment of HRQL [14], although in the present study, it proved to be valid for this purpose. As for the CS-16 and CS-31, as they are multidimensional, they allow more in-depth analysis of adverse effects and general HRQL. Even though assessments of general HRQL may serve a purpose, knowing details that permeate the HRQL of these women, certainly, can be useful in clinical management. We identified superior psychometric properties of CS-31 over CS-16, which may be related both to the characteristics of sample and to the greater number of items presented in the first. Furthermore, the CS-16 does not include any item related to symptoms in the musculoskeletal system, and aching in muscles and joints is one of the main adverse effects of AI use [24].

We identified higher scores for anxiety and depression in women with worse HQRL and improvement in HRQL over the study. Recently, Martino and collaborators [25] identified that after 6 months of treatment with AI, BC patients presented a significantly higher perceived HRQL for both physical and mental components, added to a significant reduction of anxious and depressive symptoms, possibly due to the decline of the physical and psychological effects of recent diagnosis and previous treatments [25].
Regarding Sexual and Couple domains of CS, as well as Social/Family Well-Being of FACIT-F, the latter which also presents items related to sexual life and couple relation, have not changed over time. Often, the adverse effects of treatment, as well as induced menopause, cause sexual dysfunction among BC survivors, with relevant impact on sexual function [26]. The disturbances in sexual life are among the factors that might deteriorate quality of life in BC patients and survivors [27]. The adjuvant endocrine therapy, especially AI, can cause vaginal atrophy [28], dryness and dyspareunia [4], and some urogenital effects, such as vaginal dryness, persist lifelong if untreated [29]. Possibly, the treatment has a more lasting impact on sexuality and a longer follow-up would be necessary to investigate changes in these domains. The main recommendation for the management of sexual health in BC survivors is that a multidisciplinary team needs to include the sexuality as an integral part of treatment, contributing to an improvement of HRQL [26].

We hypothesized that constructs indirectly related as Sexual and Couple of CS with Social/Family Well-Being of FACIT-F should present moderate correlation. However, this expected correlation has not been achieved by CS-16. Probably, due to the greater number of items investigated, the CS-31 is more sensitive to capture nuances that involve the sexual function and couple relation. It should be noted that sexuality is considered a biopsychosocial concept, and therefore it is believed to be associated with biological and psychosocial factors [30].

We must recognize that our study has some limitations as a small sample size. Several correlations were weak and could have become significant with larger sample sizes. Even though the CS was not designed for this population, these women are considered BC survivors, i.e. currently free of the disease, and have predominantly adverse effects like to those of other postmenopausal women, although intensified by the AI use. We need to consider that the CS’ target population is women aged 45 to 64 years [9] and our sample includes women aged 47 to 79 years. For this purpose, we divided women into two age groups (47 to 64 and 65 to 79 years) and observed that age had no effect on the CS scores by performing the Generalized Linear Model (GLzM) analysis (data not shown). In addition, the CS is a self-reported questionnaire, however in this study, all participants replied by interview, which may have inhibited responses to items in the Sexual and Couple domains. Even so, the standardization for this type of application was a methodological care considering that in our sample there were illiterate women.

As pointed out by others [13], we identified that most of invalid questionnaires were filled by women that were not married or without a partner, referring to a sexually inactive life. In fact, it was the reason for the sample difference between CS-31 and CS-16, considering that the first present more items in these domains. This seems to be a limitation of the multidimensional CS, and adaptations to these instruments are necessary to contemplate all climacteric women, irrespective of their marital status and sexual activity.

The strengths of the current research include that our study has evaluated the psychometric properties of the three CS at the same time and used them to assess HRQL at three time points, with a 2-year follow-up.

Adjuvant endocrine therapy adherence is suboptimal in BC patients. It is negatively associated with treatment adverse events [8] and associated with increased early tumor recurrence and mortality rates [31]. Potentially, clinical interventions to manage these adverse effects may improve HRQL and BC outcomes [32]. Future studies are necessary to confirm whether the implementation of CS in routine medical oncology is able to contribute to improvements in HRQL and in prognosis of these women. Even so, we suggest that CS-31 is used in outpatient service to investigate HRQL and the CS-10 to early screening of adverse effects or to population studies that seek to investigate HRQL in BC patients in AI use, as it is the fastest to apply. We believe that the use of CS can optimize the attendance time and the health outcomes, since physicians could focus on individual adverse effects and monitor, through graphic summaries, the evolution of these effects after specific interventions.

5. Conclusions

We identified that the CS, highlighting the CS-31, proved to be an appropriate option for use in routine medical oncology with BC survivors during adjuvant endocrine therapy, although larger studies are needed to confirm these results.
Abbreviations

BC Breast cancer

HR+ Hormone receptor-positive

AI Aromatase Inhibitors

HRQL Health-related quality of life

CS Cervantes Scale

PRO Patient-reported outcome

CS-31 31-item Cervantes Scale

CS-16 16-item Cervantes Short-Form Scale

CS-10 10-item Cervantes Scale

T0 Initial follow-up period

T1 Intermediate follow-up period, 12 months after T0

T2 Final follow-up period, 24 months after T0

FACIT-F Functional Assessment of Chronic Illness Therapy – fatigue

HADS Hospital Anxiety and Depression Scale

FACT-G Functional Assessment of Cancer Therapy-General

TOI Trial Outcome Index

HADS-A Hospital Anxiety and Depression Scale, subscale anxiety

HADS-D Hospital Anxiety and Depression Scale, subscale depression

GLzM Generalized Linear Model

Declarations

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Figures
Figure 1

Diagram reporting the number of women recruited and selected in the study, and the Cervantes’ sample. Legend: Time point: T0, Initial follow-up period; T1, Intermediate period, corresponding to 12 months after T0; and T2, Final follow-up period, corresponding to 24 months after T0; CS-31: 31-item Cervantes Scale; CS-16: 16-item Cervantes Short-Form Scale; CS-10: 10-item Cervantes Scale.
Figure 2

Items contained in the 31-item Cervantes Scale (CS-31), 16-item Cervantes Short-Form Scale (CS-16) and 10-item Cervantes Scale (CS-10).