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Cancer symptom clusters, cardiovascular risk, and quality of life of patients with cancer undergoing chemotherapy

A longitudinal pilot study

Karolini Zuqui Nunes, PhD, RN[a], Wesley Rocha Grippa, PhD, BSc Mathematics and Statistics[b], Andressa Bolsoni Lopes, PhD, RN[a], Karoline Neumann Gomes, RN[a], Jonathan Grassi, BSc in Audiology and Speech Language Pathology, MPH[b], Luiz Claudio Barreto Silva Neto, BSc in Nutrition and Dietetics[a], Julia Anhoque Cavalcanti Marcarini, BSc in Nutrition and Dietetics[a], Samantha Moreira Felonta, RN[c], Katia Cirlene Gomes Viana, RN[d], Luís Carlos Lopes-Júnior, PhD, RN[a,b,c,*]

Abstract

Patients with cancer undergoing chemotherapy may have different cancer symptom clusters (CSC) that negatively impact their quality of life (QoL). These symptoms can sometimes arise from the disease itself or as a result of their cancer treatment. This study aimed to: examine the feasibility of longitudinal testing of CSC pattern and QoL in a sample of adult cancer patients undergoing outpatient chemotherapy; to identify the cardiovascular risk of patients with cancer undergoing outpatient chemotherapy; and to investigate the most prevalent CSC and their impact on the QoL of these patients. A longitudinal pilot study was conducted with eleven participants with a mean age of 56.09 years (range: 27–79) diagnosed with malignant neoplasm and undergoing outpatient chemotherapy treatment were evaluated during 6 cycles of chemotherapy. The CSC, cardiovascular risk, and QoL were assessed using the MSAS, FRS, and EQ-5D-3L™, respectively. Descriptive statistical and non-parametric bivariate analyses were performed. Patients who started chemotherapy treatment generally had a low to moderate cardiovascular risk and were likely to have a family history of hypertension, acute myocardial infarction, and stroke. Cardiovascular risk was found to be correlated with patient age (*Rhos* = 0.64; *P* = .033). In addition, the results showed a reduction in the QoL scoring over the 6 chemotherapy sessions. Regarding the most prevalent CSC, 2 clusters were identified: the neuropsychological symptom cluster (difficulty concentrating-sadness-worry) and the fatigue-difficulty sleeping cluster. Between the first and sixth chemotherapy sessions, there was a decrease in the perception of "mild" severity (*P* = .004) and an increase in the perception of "severe" and "very severe" (*P* = .003) for all symptoms. Adequate attention to CSC should be the basis for the accurate planning of effective interventions to manage the symptoms experienced by cancer patients.

Abbreviations: CT = chemotherapy, EQ-5D-3L™ = EuroQol 5 dimensions and 3 levels, MSAS™ = Memorial Symptom Assessment Scale.

Keywords: cancer patients, cancer symptom clusters, cardiovascular risk, chemotherapy, quality of life

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The datasets generated during and/or analyzed during the current study are publicly available.

This study involves human participants and was approved by an Ethics Committee or Institutional Board – Centro de Ciências da Saúde da Universidade Federal do Espírito Santo – (CEP/CCS/UFES) and approved under opinion no. 4122,342, in accordance with the relevant guidelines from the Declaration of Helsinki and the ethical principles in the National Health Council of Brazil.

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[a] Graduate Program in Nutrition and Health, Health Sciences Center at the Federal University of Espírito Santo (UFES), Vitoria, ES, Brazil, [b] Graduate Program in Public Health, Health Sciences Center at the Federal University of Espírito Santo (UFES), Vitoria, ES, Brazil, [c] Nursing Department, Health Sciences Center at UFES, Vitoria, ES, Brazil, [d] Afecc-Hospital Santa Rita de Cássia, Vitoria, ES, Brazil.

** Correspondence: Luís Carlos Lopes-Júnior, Graduate Program in Public Health at the Federal University of Espírito Santo (UFES), Av. Marechal Campos, 1468 – Maruípe, Vitória, ES 29.043-900, Brazil (e-mail: lopesjr.lc@gmail.com).*

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1. Introduction

Cancer is considered a chronic noncommunicable disease (NCD) and is responsible for approximately 74% of deaths worldwide. Among NCDs, cancer is responsible for the second-highest death rate, corresponding to 9.3 million deaths.[1] The latest report on the estimated incidence and mortality from cancer of GLOBOCAN 2020 by the International Agency for Research on Cancer estimated 19.3 million new cases and 10 million deaths from cancer worldwide in the year 2020.[2]

Patients with cancer that undergo antineoplastic treatment may present with several simultaneous symptoms called cancer symptom clusters, which sometimes arise from the disease itself or as a consequence of the treatment. Chemotherapy is commonly used as an intervention for various stages of the disease.[3] Clinical practice shows that symptoms rarely occur separately but form groups that share common underlying mechanisms in terms of severity, creating a synergistic effect between them, which may even lead to predicting the development of future symptoms.[4] In addition, as the number of cancer survivors increases, cardiotoxicity associated with cancer treatment has become a great concern, posing a substantial challenge in the follow-up of these patients.[5]

While it is important to identify clusters that are consistent across cancer types and treatments, it is equally important to identify unique clusters for specific cancers and/or treatments. Studies on cancer symptom clusters have evaluated changes in clusters longitudinally, generally considering 3 or 4 points during cancer treatment.[6–14] Regarding the stability of cancer symptom clusters between their dimensions and/or across the treatment, it is expected that 75% of symptoms in the same cluster must be in line for a cluster of symptoms to be stable across time points or dimensions.[15]

For example, patients with breast cancer undergoing chemotherapy can experience up to 8 symptoms simultaneously, such as pain, anxiety, fatigue, lack of appetite, emotional distress, drowsiness, depression, and nausea. The average severity of these symptoms varies between people.[16] In addition, cancer symptom clusters interfere with an individual's quality of life (QoL),[17] making it essential to assess the quality of oncology services. Identifying these factors helps understand the physiology, choose an appropriate treatment, and improve patients' QoL.[18]

In addition to identifying clusters, it is essential to elucidate sociodemographic and clinical variables of epidemiological importance.[19] The social and demographic aspects of patients with cancer are of great importance in the epidemiology of cancer, such as the age of patients, as such information provides information on the natural history of the disease.[20] Moreover, to successfully treat these patients, the joint and collaborative work of different professionals that make up multidisciplinary and interdisciplinary teams is required to improve the health outcomes of patients with cancer.[21,22]

Hence, the present study aimed to examine the feasibility of longitudinal tests of CSC pattern and the QoL of patients with cancer undergoing outpatient chemotherapy, identify the cardiovascular risk of patients with cancer undergoing outpatient chemotherapy, and investigate the most prevalent CSC and their impact on the QoL of these patients.

2. Methods

2.1. Study design

This was a longitudinal pilot study conducted at the Afecc-Hospital Santa Rita de Cássia (Afecc-HSRC), a comprehensive cancer care center for cancer treatment located in the state of Espírito Santo, Southeast Region of Brazil. The Afecc-HSRC is a philanthropic entity, a partner of the services that care for the population via the Unified Health System (SUS), and allocates more than 60% of health care services to the public.

2.2. Ethical issues

This study was approved by the Institutional Review Board of the Health Sciences Center at the Federal University of Espírito Santo (UFES), and approval was obtained under Opinion Number 4122,342, respecting the guidelines and regulatory norms for research involving human beings in Brazil established by Resolution 466/2012. Permission for the data collection was obtained and approved by the hospital institution (Afecc-HSRC).

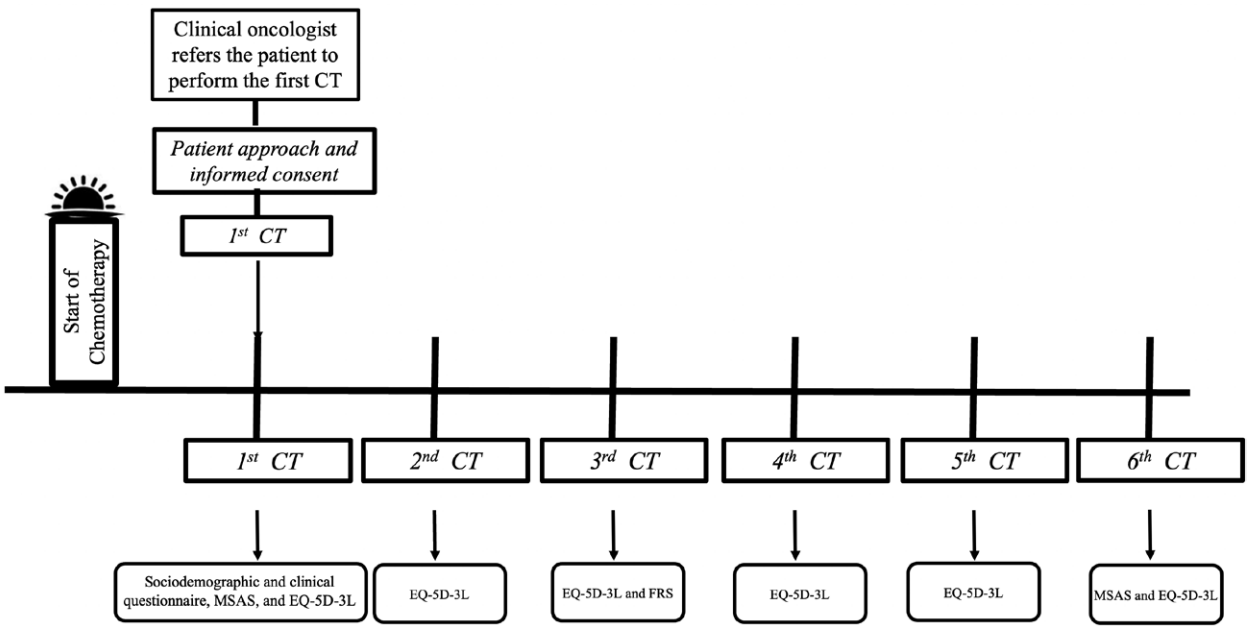

Figure 1. Data collection flowchart. CT = chemotherapy, ERF™ = Framingham Risk Score, EQ-5D-3L™ = EuroQol 5 dimensions and 3 levels, MSAS™ = Memorial Symptom Assessment Scale.

2.2.1. Participants. Patients who met the following eligibility criteria were included: age > 18 years; anatomopathological diagnosis of malignant neoplasm at any stage (I to III); and patients (only new cases) undergoing outpatient chemotherapy at the time of data collection with a schedule of at least 6 chemotherapy sessions. The exclusion criteria established for this study were as follows: patients with cancer recurrence and patients in stage IV; with any cognitive impairment that prevented the understanding of the data collection instruments.

2.3. Data collection procedures

Data were collected from September 2021 to December 2021. Initially, the schedules of clinical oncologists at Afecc-HSRC were analyzed to identify potential patients scheduled for a first-time indication for chemotherapy treatment. After consultation with the clinical oncologist and after the patient was referred to the chemotherapy sector to schedule it, the patient was initially approached to ascertain whether they would consent to participate in the research, according to the eligibility criteria. The research objectives were presented at this first meeting, and an informed consent form was signed.

It is noteworthy that data collection was carried out at the Chemotherapy Outpatient Clinic of Afecc-HSRC by 2 professors who are nurses and specialists in Oncology as well as researchers from the Research Group in Oncology at UFES. Patients were approached at the outpatient clinic in a private place and individually to answer the instruments.

Figure 1 shows the data collection scheme used in this study.

2.3.1. Instruments for data collection.

2.3.1.1. Sociodemographic and clinical characterization. A sociodemographic and clinical questionnaire prepared by the main researcher was administered to obtain the baseline data of the eligible patients based on the Tumor Form of the Hospital-Based Cancer Registry of the referred hospital. Data from this questionnaire included age, marital status, education, occupation, ethnicity, height, weight, BMI, body surface area, date of cancer diagnosis, type and stage of cancer, chemotherapy protocol, preexisting diseases, and cardiovascular risk factors. Data were obtained through the Hospital-Based Cancer Registry and the patient's medical records.

2.4. MSAS

The Memorial Symptom Assessment Scale (MSAS), developed by Portenoy et al (1994),[23] helps detect and monitor multiple symptoms in patients with cancer. This instrument combines different symptoms and their respective degrees of severity, frequency, and distress. It is a self-report instrument in which patients assign a numerical value from 1 to 4 points to the frequency and severity of 32 symptoms and from zero to 4 points to the degree of distress experienced during the previous week. In addition, it is divided into subscales that assess psychological symptoms (PSYCH) with 6 items and physical symptoms (PHYS H and PHYS L) with 26 items. The internal consistency of these groups was evaluated in the original version using Cronbach's alpha coefficient, and the following values were assigned: PSYCH (0.835), PHYS H (0.882), and PHYS L (0.580).[23]

A recent study that aimed to evaluate the test-retest reliability of the translated and culturally adapted Brazilian Portuguese version of the MSAS suggested that the reliability of the scale was satisfactory.[24] The weighted kappa values obtained for each item on the scale were adequate, with the highest item being 0.96 and the lowest being 0.69. The kappa of the subscales was also evaluated. It was found to be 0.84 for high-frequency physical symptoms, 0.81 for low-frequency physical symptoms, 0.81 for psychological symptoms, and 0.78 for the general index of suffering, respectively. The authors concluded that the high levels of reliability estimated allowed us to state that the process of measuring the MSAS items was adequate.[24] The MSAS collection time chosen for this pilot study was the

Table 1

Sociodemographic and past characterization of patients with cancer undergoing outpatient chemotherapy.

		N	%
Sex	Male	2	18.2
	Female	9	81.8
Age range	25–29	1	8.3
	45–49	2	16.7
	50–54	2	16.7
	55–59	2	16.7
	60–64	1	8.3
	65–69	1	8.3
	70–74	1	8.3
	75–79	1	8.3
Self-reported color	White	3	27.3
	Black	2	18.2
	Brown	6	54.5
Marital status	Single	2	18.2
	Married	7	63.6
	Widower	1	9.1
	Divorced	1	9.1
Source of income	Employee	4	36.4
	No income	3	27.3
	Retiree	3	27.3
	Pensioner	1	9.1
Education	Illiterate	0	0.0
	Incomplete Elementary	4	36.4
	Complete Elementary	3	27.3
	Incomplete High School	0	0.0
	Complete High School	3	27.3
	Incomplete Higher	1	9.1
	Graduated	0	0.0
Occupation	Hairdresser	1	9.1
	Dressmaker	1	9.1
	From home	2	18.2
	Tour guide	1	9.1
	Teacher	1	9.1
	Chef	1	9.1
	Autonomous	1	9.1
	Driver	1	9.1
	Retiree	1	9.1
	Farmer	1	9.1
Health insurance	No	9	81.8
	Yes	2	18.2
Reason for looking for the Oncology Referral service	Forwarding	3	27.3
	Start of treatment	6	54.5
	No information	2	18.2
Family history of cancer	No	3	27.3
	Yes	8	72.7
Degree of kinship	First degree	1	9.1
	Second degree	3	27.3
	Third degree	1	9.1
	First and second degree	1	9.1
	First and third degree	1	9.1
	Second and third degree	1	9.1
	No information	3	27.3
Heart disease	No	9	81.8
	Yes	2	18.2
AMI	No	7	63.6
	Yes	4	36.4
DM	No	8	72.7
	Yes	3	27.3
SAH	No	5	45.5
	Yes	6	54.5
Stroke	No	7	63.6
	Yes	4	36.4

AMI = acute myocardial infarction, DM = diabetes mellitus, SAH = systemic arterial hypertension.
*CIB/SUS-ES Resolution No. 153/2020, SESA/ES.

first chemotherapy session and the sixth chemotherapy session, as the MSAS assesses symptoms with reference to the previous week. Thus, we intend to evaluate both the symptoms caused by cancer without the influence of chemotherapy (before receiving the 1st CT) and also by chemotherapy treatment (in the 6th CT session) and compare.

It should be highlighted that the symptoms we intend to evaluate are those caused by cancer and also by chemotherapy treatment, and therefore, we chose to use the MSAS, which is used worldwide to evaluate symptoms in cancer patients.

2.5. Cardiovascular risk questionnaire

The FRS is a scale used to assess the cardiovascular risk of each patient. Based on sex, age, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, BP, diabetes mellitus, and smoking, it is possible to establish a person's risk of developing coronary artery disease in the next 10 years. Each risk factor has a specific score, and the sum of the points provides the global score of each individual. Through this score, it is possible to classify patients as low risk (<10%), medium risk (greater than 10%, but less than 20%), and high risk (>20%).[25] Since the Framingham Risk Score (FRS) is used to stratify cardiovascular risk in 10 years, we have chosen to standardize the application of this instrument at the unique data collection point (3rd).

2.6. EQ-5D-3L™

EQ-5D is a generic instrument for measuring health-related QoL, which allows the generation of an index representing the value of an individual's health status. Developed by the EuroQoL group in 1987[26] and made public in 1990,[27] it is based on a classification system that describes health in 5 dimensions: mobility, personal care, usual activities, pain/illness being, and anxiety/depression. Each of these dimensions has 3 associated severity levels corresponding to no problems (Level 1), some problems (Level 2), and extreme problems (Level 3) experienced or felt by the individual. Therefore, this system allows the description of $3^5 = 243$ distinct health states.[27] EQ-5D™ provides a simple description and a single index value for possible health states. The questionnaire has 2 versions that vary in the number of options for grading the severity of each dimension: EQ-5D-5L and EQ-5D-3L. The questionnaire consisted of a descriptive system and visual analog scale. The parameters of different nationalities for health status were valued, allowing adjustments in the preferences of each population, including the Brazilian population.[28] The visual analog scale records the interviewee's self-perception of health on a scale in which their extremities are displayed as "best imaginable health state" and "worst imaginable health state."

Cancer is one of the most frequent disease-specific applications of the EQ-5D-3L™. The EQ-5D-3L™ is advantageous because it is easy to apply and understand and can be performed via telephone.[27,29,30] Previous studies have shown good reliability of the EQ-5D-3L™ (EuroQol 5 dimensions and 3 levels) based on information provided by relatives.[30–32] In addition, the Portuguese version of the EQ-5D showed good acceptability, reliability, and validity in measuring health status (Cronbach's alpha coefficient = 0.716).[28] In the present pilot study, the EQ-5D-3L was collected at the first, second, third, fourth, fifth, and sixth chemotherapy sessions, as it is a simple scale that is easy for the patient to complete, not requiring much effort. All patients completed this scale in less than 5 minutes.

Table 2

Clinical characteristics of patients with cancer undergoing outpatient chemotherapy.

		N	%
ICD-10	C53.9 – Malignant neoplasm of cervix	2	18.2
	C50.8 – Malignant breast neoplasm with invasive lesion	6	54.5
	C18.9 – Malignant neoplasm of colon, unspecified	3	27.3
Other primary cancers	No	11	100.0
	Yes	0	0.0
Metastasis	No	11	100
Histological type of primary tumor	Squamous cell carcinoma, NFS	2	18.2
	Adenocarcinoma, NFS	3	27.3
	Infiltrating ductal carcinoma, NFS	6	54.5
TNM	T3N1M0	1	9.1
	T2N1M0	4	36.4
	T3N0M0	2	18.2
	T2N0M0	2	18.2
	T4N1M0	2	18.2
Clinical staging of the tumor	I	1	9.1
	II	6	54.5
	III	4	36.4
	IV	0	0.0

ICD = International Statistical Classification of Diseases and Related Health Problems, NFS = not further specified, TNM = Classification of Malignant Tumors (T= Tumor; N= Lymphnodes; M= Metastasis).

2.7. Data analysis

Descriptive statistical analyses (calculation of absolute and percentage frequencies, mean, standard deviation, and minimum and maximum values) were performed using the IBM Statistical Package for the Social Sciences – SPSS software, version 28.0 (SPSS, Inc., Chicago, IL).

In cluster analyses, the K-means algorithm[33] was used to build the cluster graph (a type of unsupervised learning among machine learning techniques), and the characteristic used in the grouping was the distance. For the dendrogram, hierarchical grouping was performed using the Euclidean distance to separate the groups.[34] To verify the difference in the QoL between chemotherapy sessions, the Wilcoxon non-parametric test was used.[35] Spearman's correlation test was used to verify the existence of variables associated with the FRS. All analyses were performed using RStudio software version 2022, combined with R software version 4.1.0, and the significance level adopted was 5%.

3. Results

The demographic characteristics and histories of the participants are summarized in Table 1. The mean age of the participants was 56.09 years old, with a standard deviation (SD) = ±

Table 3

Framingham score of patients with cancer undergoing outpatient chemotherapy.

Sex	Scoring	CAD risk at 10 years, %
Female	13	17
Female	11	13
Female	5	5
Female	9	9
Female	13	17
Female	6	6
Female	11	13
Female	–14	1
Female	7	7
Male	8	18
Male	8	18

CAD = coronary artery disease.

14.23 (27–79 years old). About 36% had some type of allergy, 2 (18.2%) of which were drug-related. In addition, all patients had undergone some type of surgery, with an emphasis on gynecological surgery; that is, 3 (27.3%) females in the sample had previously undergone cesarean sections. Among the patients, the majority (6; 54.5%) were sedentary.

Patients with systemic arterial hypertension (SAH) represented 18.2% of the participants. In addition, only 1 (9.1%) participant had chronic obstructive pulmonary disease, 1 (9.1%) dyslipidemia, 1 (9.1%) pericarditis, and 1 (9.1%) obesity. According to the participant's family history, 8 (72.7%) had a family history of cancer, with prostate cancer being the most frequent, accounting for 18.2%, and most were second-degree relatives (3; 27.3%). Most of the patients had a family history of comorbidities, with SAH as the main comorbidity in 6 (54.5%), followed by acute myocardial infarction (AMI) and cerebral vascular accident in 4 (36.4%) of the subjects. The clinical characteristics of the patients are shown in Table 2.

The diagnosis of malignant neoplasm of the breast with invasive lesions comprised 54.5% and 27.3% of malignant neoplasm of colon. Approximately 54.5% of the patients had clinical stage II tumors.

Table 3 presents the cardiovascular risk classification of the patients according to the Framingham Risk Score (FRS). It was shown that 6 (54.55%) patients with cancer that underwent chemotherapy in our sample had moderate cardiovascular risk, and another 5 (45.45%) patients had low cardiovascular risk. No patient had a high cardiovascular risk according to their scores.

Information on the QoL of patients with cancer undergoing outpatient chemotherapy according to the EQ-5D-3L is shown in Table 4. The QoL was found to decrease during treatment. The current total QoL score at the first chemotherapy session was 86, whereas at the sixth session, it was 68. Domain 5 (anxiety and depression) was the most frequent and impacted, followed by domain 4 (pain and distress), with a decline observed from the first to the sixth chemotherapy session. Domain 3 (habitual activity) increased in frequency throughout treatment. At the first chemotherapy session, only 1 (9.1%) participant reported problems in performing usual activities, and 3 (27.3%) had problems in this domain at the sixth chemotherapy session.

When checking whether there was a difference in QoL between the first and sixth chemotherapy sessions based on the Wilcoxon test (paired), no statistically significant difference was found for any interval between sessions 1 and 5, with *P* values close to 1; however, when comparing 1 CT with 6 CT, a statistically significant difference was detected that is, there was a significant deterioration in QoL in the 6 CT session, as can be seen in Supplementary Material 1, http://links.lww.com/MD/M188.

The prevalence and severity of the symptoms are listed in Table 5. All patients had concomitant symptoms. The most frequent symptoms at the first session were difficulty concentrating (7; 63.63%), sadness (7; 63.63%), worry (7; 63.63%), lack of energy (6; 54.54%), and prison belly (6; 54.54%). Less frequent symptoms were numbness (1; 9.09%), vomiting (1; 9.09%), shortness of breath (1; 9.09%), sweating (1; 9.09%), itching (1; 9.09%), difficulty swallowing (1; 9.09%), mouth sores (1; 9.09%), change in food taste (1; 9.09%), and skin changes (1; 9.09%). The most frequent symptoms at the sixth chemotherapy session were lack of energy (6; 54.54%), worry (6; 54.54%), dry mouth (5; 45.45%), difficulty sleeping (5; 45.45%), loss of hair (5; 45.45%) and "I don't look the same anymore" (5; 45.45%). Less frequent symptoms were sweating (1; 9.09%), problems with sexual desire (1; 9.09%), mouth sores (1; 9.09%), and swelling (1; 9.09%).

At the first chemotherapy session, none of the patients showed symptoms of diarrhea, hair loss, or swelling. None reported cough, vomiting, or shortness of breath at the sixth chemotherapy session. The symptoms that increased in frequency from the first chemotherapy session to the sixth session were hair loss (5;

Table 4

Quality of life of patients with cancer undergoing outpatient chemotherapy according to EQ-5D-3L.

CTs	D1: Mobility			D2: Personal care			D3: Habitua activities			D4: Pain/distress			D5: Anxiety/depression			
3L	I have no problems, n (%)	Some problems, n (%)	I am unable, n (%)	I have no problems, n (%)	Some problems, n (%)	I am unable, n (%)	I have no problems, n (%)	Some problems, n (%)	I am unable, n (%)	No pain, n (%)	Moderate pain, n (%)	Extreme pain, n (%)	I have no problems, n (%)	Some problems, n (%)	Highly anxious and depressed, n (%)	QoL Score
1st CT	10 (90.9)	1 (9.1)	0 (0)	10 (90.9)	1 (9.1)	0 (0)	10 (90.9)	1 (9.1)	0 (0)	5 (45.5)	6 (54.5)	0 (0%)	4 (36.4)	7 (63.6)	0 (0)	86
2nd CT	9 (81.8)	2 (18.2)	0 (0)	10 (90.9)	1 (9.1)	0 (0)	11 (100)	0 (0)	0 (0)	5 (45.5)	6 (54.5)	0 (0)	4 (36.4)	6 (54.5)	1 (9.1)	83
3rd CT	9 (81.8)	2 (18.2)	0 (0)	10 (90.9)	1 (9.1)	0 (0)	9 (81.8)	2 (18.2)	0 (0)	8 (72.7)	2 (18.2)	1 (9.1)	5 (46)	5 (46)	1 (9.1)	82.55
4th CT	11 (100)	0 (0)	0 (0)	11 (100)	0 (0)	0 (0)	9 (81.8)	2 (18.2)	0 (0)	8 (72.7)	3 (27.3)	0 (0)	4 (36.4)	6 (54.5)	1 (9.1)	84
5th CT	11 (100)	0 (0)	0 (0)	10 (90.9)	1 (9.1)	0 (0)	8 (72.7)	3 (27.3)	0 (0)	7 (63.6)	3 (27.3)	1 (9.1)	5 (46)	5 (46)	1 (9.1)	80
6th CT	10 (90.9)	1 (9.1)	0 (0)	11 (100)	0 (0)	0 (0)	7 (63.6)	3 (27.3)	1 (9.1)	6 (54.5)	4 (36.4)	1 (9.1)	4 (36.4)	6 (54.5)	1 (9.1)	68

CT = chemotherapy, D = domains, L = EQ-5D-3L scale degrees.

Table 5

Prevalence of symptoms in patients with cancer undergoing outpatient chemotherapy according to the MSAS.

	1st chemotherapy					6th chemotherapy				
	Prevalence		Frequency	Severity	Distress	Prevalence		Frequency	Severity	Distress
Symptoms	n	%	M ± SD	M ± SD	M ± SD	n	%	M ± SD	M ± SD	M ± SD
Difficulty concentrating	7	63.64	2.14 ± 0.90	1.14 ± 0.78	1.66 ± 1.50	4	36.36	2.00 ± 0.81	1.75 ± 0.50	2.00 ± 1.00
Pain	4	36.36	2.00 ± 0.81	1.75 ± 0.50	3.00 ± 1.15	3	27.27	2.33 ± 1.52	2.33 ± 0.57	3.00 ± 1.73
Lack of energy	6	54.55	2.66 ± 1.21	2.16 ± 1.17	3.33 ± 1.50	6	54.55	2.00 ± 1.41	2.16 ± 1.17	3.00 ± 1.26
Cough	2	18.18	2.00 ± 1.41	1.50 ± 0.70	3.00 ± 2.82	0	0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Nervousness	5	45.45	3.00 ± 1.00	1.80 ± 0.83	3.60 ± 1.14	3	27.27	2.66 ± 1.15	3.00 ± 1.00	3.33 ± 1.52
Dry mouth	3	27.27	1.33 ± 0.57	1.00 ± 0.00	2.33 ± 0.57	5	45.45	1.80 ± 1.30	1.14 ± 0.89	2.00 ± 1.22
Nausea	2	18.18	2.50 ± 0.70	1.00 ± 0.00	2.00 ± 0.00	2	18.18	2.00 ± 1.41	2.00 ± 0.00	3.50 ± 2.12
Drowsy	3	27.27	1.66 ± 0.57	1.33 ± 0.57	3.00 ± 1.73	3	27.27	1.66 ± 1.15	1.66 ± 0.57	2.00 ± 0.00
Numbness	1	9.09	1.00 ± 0.00	1.00 ± 0.00	3.00 ± 0.00	3	27.27	2.66 ± 1.52	2.00 ± 1.00	2.33 ± 1.52
Difficult sleeping	5	45.45	3.40 ± 1.34	2.60 ± 0.54	3.60 ± 1.14	5	45.45	3.40 ± 0.89	2.60 ± 0.54	3.00 ± 1.87
Bloated	3	27.27	2.33 ± 1.53	1.33 ± 0.57	3.33 ± 1.52	3	27.27	2.66 ± 0.57	2.33 ± 1.15	3.00 ± 1.73
Problems with urination	2	18.18	3.00 ± 1.41	2.00 ± 0.00	2.50 ± 0.70	2	18.18	4.00 ± 0.00	2.00 ± 0.00	2.00 ± 1.41
Vomiting	1	9.09	1.00 ± 0.00	1.00 ± 0.00	2.00 ± 0.00	0	0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Shortness of breath	1	9.09	2.00 ± 0.00	1.00 ± 0.00	2.00 ± 0.00	0	0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Diarrhea	0	0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	2	18.18	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00
Sadness	7	63.64	2.00 ± 0.57	1.57 ± 0.53	2.71 ± 1.38	3	27.27	3.33 ± 1.15	3.00 ± 1.00	4.00 ± 1.73
Sweating	1	9.09	2.00 ± 0.00	2.00 ± 0.00	5.00 ± 0.00	1	9.09	0.00 ± 0.00	3.00 ± 0.00	4.00 ± 0.00
Worrying	7	63.64	3.42 ± 1.13	2.28 ± 1.11	3.28 ± 1.38	6	54.55	2.83 ± 0.98	2.33 ± 1.03	3.16 ± 1.60
Problems with desired/sexual activity	2	18.18	2.50 ± 0.70	1.50 ± 0.70	2.50 ± 0.70	1	9.09	4.00 ± 0.00	4.00 ± 0.00	5.00 ± 0.00
Itching	1	9.09	3.00 ± 0.00	2.00 ± 0.00	3.00 ± 0.00	2	18.18	2.00 ± 0.00	1.50 ± 0.70	1.50 ± 0.70
Lack of appetite	4	36.36	2.00 ± 0.81	1.75 ± 0.50	3.25 ± 1.50	3	27.27	3.00 ± 1.00	3.00 ± 1.00	5.00 ± 0.00
Dizziness	3	27.27	2.33 ± 1.15	1.66 ± 0.57	3.00 ± 1.00	4	36.36	3.00 ± 0.81	2.50 ± 1.00	4.00 ± 1.41
Difficulty swallowing	1	9.09	4.00 ± 0.00	2.00 ± 0.00	3.00 ± 0.00	2	18.18	2.5 ± 2.12	1.50 ± 0.70	3.50 ± 2.12
Irritable	3	27.27	2.66 ± 1.15	1.66 ± 0.57	3.66 ± 1.52	3	27.27	2.66 ± 1.15	2.33 ± 1.52	3.33 ± 1.52
Mouth sores	1	9.09	3.00 ± 0.00	2.00 ± 0.00	3.00 ± 0.00	1	9.09	3.00 ± 0.00	2.00 ± 0.00	3.00 ± 0.00
Change in food taste	1	9.09	1.00 ± 0.00	2.00 ± 0.00	4.00 ± 0.00	2	18.18	4.00 ± 0.00	3.00 ± 1.41	5.00 ± 0.00
Weight loss	3	27.27	1.00 ± 0.00	1.00 ± 0.00	1.66 ± 0.57	3	27.27	1.00 ± 0.00	1.33 ± 0.57	1.66 ± 0.57
Hair loss	0	0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	5	45.45	3.40 ± 0.54	3.40 ± 0.89	2.25 ± 1.89
Constipation	6	54.55	1.83 ± 1.17	1.50 ± 0.83	3.50 ± 1.37	2	18.18	2.00 ± 1.41	2.50 ± 0.70	4.50 ± 0.70
Swelling of arms or legs	0	0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	1	9.09	2.00 ± 0.00	2.00 ± 1.00	1.00 ± 0.00
I don't look like myself	4	36.36	1.50 ± 0.57	1.25 ± 0.50	2.50 ± 1.29	5	45.45	2.80 ± 1.30	2.40 ± 0.89	2.80 ± 1.30
Skin changes	1	9.09	3.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	3	27.27	1.66 ± 1.15	2.00 ± 0.00	2.33 ± 0.57

CT = chemotherapy, M ± SD = Mean ± Standard Deviation.

45.45%), dry mouth (5; 45.45%), numbness (5; 45.45%), and "I don't look the same anymore" (5; 45.45%). Regarding the severity of symptoms, most participants reported that they were at mild and moderate levels at the first chemotherapy session. At the sixth chemotherapy session, most patients reported moderate symptoms. Regarding distress, at the first session, the majority reported "a little" distress followed by "considerably." At the sixth chemo, the majority presented symptoms at the level "a little" followed by the level "a lot." The analysis revealed 2 main symptom clusters. The first cluster consisted of neuropsychological symptoms (difficulty concentrating, sadness, and worry), and the second cluster consisted of fatigue and difficulty sleeping symptoms. The other symptoms were unstable during the 4 chemotherapy sessions and were grouped separately.

Statistically significant differences were observed in the perception of mild ($P = .004$) and severe and very severe ($P = .003$) intensities between the first and sixth chemotherapy sessions using the Wilcoxon test (paired). That is, between the first and sixth chemotherapy sessions, there was a decrease in the perception of mild severity and an increase in the perception of severe and very severe intensities for all the symptoms. Using the data clustering technique, K-means, the symptoms reported at the sixth chemotherapy session were subdivided into 4 subsets (Supplementary Material 2, http://links.lww.com/MD/M189). This subdivision can also be observed graphically in the cluster plot shown in Figure 2.

Figure 3 presents a dendrogram created from the grouping of symptoms reported by 11 adult patients diagnosed with cancer (all new cases) undergoing outpatient chemotherapy treatment and the symptoms that occurred together or independently. Hierarchical cluster analysis was used to aggregate the self-reported symptoms. Through this representation, it is possible to identify related symptoms (connected vertical lines) and the distances between them. Distance values from 0 to 8 refer to the relative distances between the symptoms, which represent the probability that they are found in the same grouping or cluster. From left to right, the data show a close relationship between the neuropsychological/affective and gastrointestinal symptom clusters. The nodes in this dendrogram represent the links between the symptoms. For example, a cluster representing difficulty sleeping and worry was more closely associated with alopecia symptoms (hair loss) than gastrointestinal and respiratory symptom clusters. A second cluster, composed of fatigue (lack of energy), was associated with symptoms such as difficulty concentrating and, consequently, sleep disorders (sleepiness). Another identified cluster comprised nervousness and irritability. These 2 clusters combine with sadness/lack of appetite and problems with desired/sexual activity/change in food taste, causing a synergistic effect between them.

A Spearman correlation matrix was used to assess possible correlations between cardiovascular risk and the variables QoL, age, weight, and body mass index (BMI). This helped to highlight a strong and direct correlation between cardiovascular risk and age (Rhos = 0.64; $P = .033$), indicating that the greater the age of patients with cancer, the greater their cardiovascular risk over the next 10 years. The other variables did not show statistically significant correlations (Table 6).

4. Discussion

This longitudinal pilot study identified that new patients who started chemotherapy treatment had, in the majority of cases, low to moderate cardiovascular risk and a family history of cardiovascular diseases. In addition, the results showed a

Figure 2. Cluster plot.

reduction in QoL during chemotherapy sessions. Regarding the cancer symptom clusters, 2 main clusters were identified: the neuropsychological symptom cluster (difficulty concentrating, sadness, and worry) and the fatigue and difficulty sleeping cluster.

4.1. Chemotherapy and cardiovascular risk

Despite advances in oncological treatment involving the use of chemotherapy, progress has also resulted in greater exposure of patients to cardiovascular risk factors due to the proven cardiotoxic effects generated by chemotherapy, particularly anthracyclines, which increase the risk of arterial hypertension, the

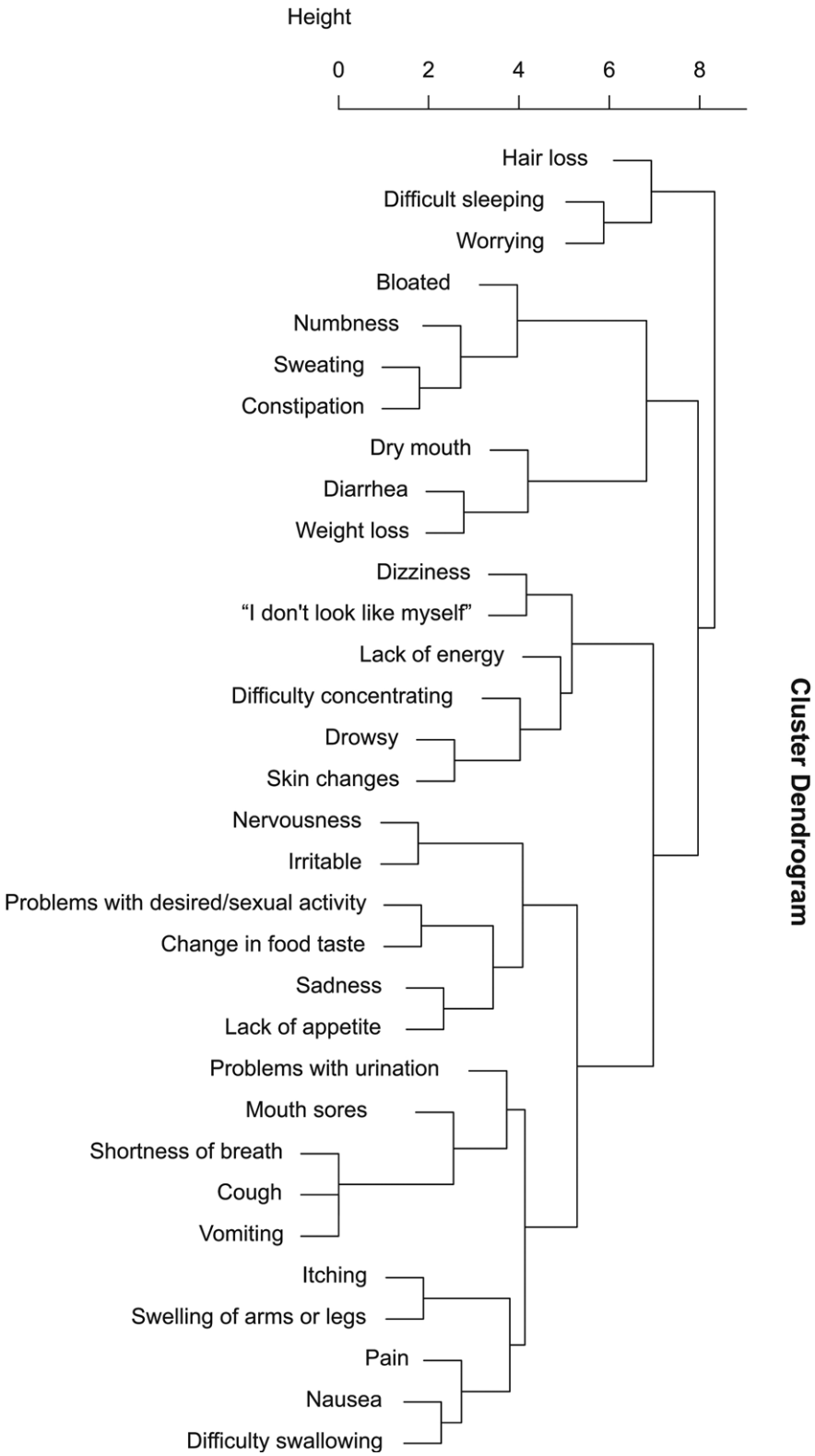

Figure 3. Symptom clusters dendogram.

Table 6

Correlation matrix.

	Framinghan Score Risk	Mean QoL score	BMI	Age	Weight
Risk	1	0.0671	−0.1189	**0.6413**	−0.022
Mean Qol Score		1	−0.1701	−0.0023	−0.3402
BMI			1	−0.2009	0.8454
Age				1	0.2236
Weight					1

Bold does mean correlation estatisticamente significante (Rhos = 0.64; $P = .033$).
BMI = body mass index, QoL = quality of life.

electrical activity of the heart, heart failure, and myocarditis, among others.[36–39] This study identified that most patients who started chemotherapy treatment had low to moderate cardiovascular risk. In addition to that, they had a family history of arterial hypertension, AMI, and stroke. Studies have shown that a family history of cardiovascular disease is consistently associated with a higher risk of developing cardiovascular disease.[40,41]

In addition to data related to cardiovascular risk and family history, it can be noted that there was a strong and direct correlation between cardiovascular risk and age, indicating that the older the patient with cancer, the greater their cardiovascular risk in the next ten years. The other variables (QoL, weight, and BMI) were not significantly correlated with cardiovascular risk. In addition, modifiable cardiovascular risk factors, such as high blood pressure (BP), have been described as potentiators of the risk associated with chemotherapy for major cardiac events in childhood cancer survivors.[42]

Thus, considering the association between the use of chemotherapy and damage to the cardiovascular system,[43–45] it is extremely important that health professionals are aware of the cardiotoxic effects of chemotherapy and use recommended strategies, such as the American Society of Clinical Oncology guidelines, to minimize potential risks, including routine assessment of clinical history, physical examination, and cardiovascular risk in cancer patient care services.[46] The presence of a cardiovascular complication can determine the interruption of chemotherapy treatment and compromise the cure or even control of cancer.[47]

4.2. Chemotherapy and QoL

QoL is an important measure of health impact and is considered an instrument for health promotion. The World Health Organization defines QoL as an individual's perception of their position in life, in the context of their value systems and culture, in relation to their goals, expectations, and interests.[48–51] The assessment of QoL during the course of health treatment has a positive effect on the well-being of individuals, their families, and their caregivers, as well as on satisfaction with treatment, as it allows obtaining important information from patients not only about the symptoms of the disease and adverse effects of the treatment but also on the psychological, social, and spiritual aspects.[52]

Numerous studies have shown that QoL parameters deteriorate due to cancer diagnosis.[52–56] The diagnosis of neoplastic disease usually causes intense anxiety, a sense of danger, insecurity, and often depression.[57] These reactions stem from the social perception that cancer is a painful and inevitably fatal disease.[50,58] In this study, we demonstrated that QoL decreased during treatment. Corroborating previous studies, domain 5 of the EQ-5D-3L, which includes anxiety and depression, was the most frequent and impacted domain, followed by domain 4 (pain and distress).

QoL largely depends on and influences the state of health; that is, the impact of the disease and treatment on the patient's physical conditioning. Therefore, evaluating the QoL allows for the identification of the different needs of the patients and, thus, the implementation of strategies that collaborate with the progression of the treatment and with the positive attitudes of the patients, which will play an important role in the recovery process.[59–61]

To obtain the best possible QoL in the context of an oncological disease, it is important to regularly monitor the different parameters of QoL, which will allow the identification of high risk patients and early intervention according to the identified needs or deficits. Undetected and untreated disorders threaten the outcomes of cancer therapies, reduce patients' QoL, and increase healthcare costs.[51]

4.3. Cancer symptom clusters

Cancer progression and its treatment can lead to the development of multiple symptoms throughout the lives of patients, including fatigue, sleep disturbances, pain, cognitive dysfunction, and anxiety. These symptoms reduce the functional status of the individual, with a consequent decrease in QoL, and may occur alone or together, constituting clusters (groupings) of symptoms.[62–71] Recognition of these symptoms and clusters is important for achieving an optimal QoL.[67,68]

In this study, the assessment of cancer symptoms using the Memorial Symptom Assessment Scale (MSAS) showed that all patients had concomitant symptoms. The most common symptoms at the first chemotherapy session were difficulty concentrating, sadness, worry, lack of energy, and constipation. In contrast, by the sixth chemotherapy session, the most common symptoms were lack of energy, worry, dry mouth, trouble sleeping, hair loss, and "I don't look the same anymore."

Although this study found that most symptoms were isolated in patients, clinical practice shows that symptoms rarely occur separately and that most of the time, they occur in a grouped manner, sharing common underlying mechanisms in terms of severity, creating a synergistic effect between them.[62,67–71]

Recent study aimed to discover the physical and psychological symptoms, using MSAS, related to chemotherapy treatment in 246 Spanish cancer patients in order to improve their quality of life.[72] The most prevalent symptoms were a lack of energy (76.4%), anxiety (66.7%), and a dry mouth (60.6%). The authors have concluded that symptom's prevalence knowledge could improve the patients' care to prevent or avoid complications and to improve the cancer patients' quality of life.[72]

The analysis also revealed 2 major symptom clusters. The first cluster consisted of neuropsychological symptoms (difficulty concentrating, sadness, and worry), and the second cluster consisted of symptoms related to fatigue and difficulty sleeping. Symptoms of sadness and worry, present in groups and isolation, are strongly associated with high levels of cytokine expression (IL-1β, IL-6, IL-10, TNF-α, INF-γ) in patients with cancer.[73–76] Other studies have shown that high concentrations of pro-inflammatory cytokines greatly contribute to the occurrence, and severity of various symptoms in patients with cancer.[77,78] These data suggest that such symptoms may contribute to the worsening of the patient's prognosis. A lack of energy and difficulty sleeping are among the most commonly reported symptoms associated with cancer and its treatment.[79] Sleep disturbance in patients with cancer is directly associated with an increased burden of symptoms and a worse QoL.[80,81]

4.4. Limitations

This pilot study represents an area of study in its early stages and has some limitations. First, it was a single-center study with only 11 participants. Second, it was a heterogeneous tumor sample. Third, the MSAS evaluates symptoms in the week prior to treatment, thus, the symptoms that patients had at the 1st

chemotherapy session may not due to chemotherapy, but related to the disease progression.

4.5. Future perspectives

This pilot study has identified groups with different symptom management needs and distinguished groups by sociodemographic/baseline clinical variables. This pilot study can help to identify patients at risk of a greater burden of symptoms as well as might have implications for the improvement of personalized nursing in the personalized cancer medicine,[82] and be used to inform future studies. In addition, the data of the expanded study will be stratified by tumor type and will take into account the chemotherapy protocol and comorbidities.

5. Conclusion

This pilot study identified that the majority of patients who started chemotherapy had low to moderate cardiovascular risk and a family history of SAH, AMI, and stroke, with the cardiovascular risk being correlated with patient age. In addition, the results showed a reduction in the QoL over the 6 chemotherapy sessions. Regarding the most prevalent cancer symptom clusters, 2 clusters were identified: a neuropsychological symptom cluster (difficulty concentrating, sadness, and worry) and a fatigue and difficulty sleeping cluster.

It was possible to confirm the feasibility of using longitudinal tests in 6 chemotherapy sessions to assess the patterns of cancer symptom clusters and QoL in a sample of adult patients with cancer. Therefore, a large-scale study using this methodology can now be conducted.

The results of this study may guide healthcare professionals in managing the symptoms of patients with cancer. Adequate attention to clusters of symptoms should be the basis for the accurate planning of effective interventions to manage the cancer symptom clusters experienced by oncological patients. Early planning may improve QoL and minimize risks for the patient, especially the risks of cardiovascular disease.

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Author contributions

Conceptualization: Karolini Zuqui Nunes, Luís Carlos Lopes-Júnior.
Data curation: Karolini Zuqui Nunes, Wesley Rocha Grippa, Andressa Bolsoni Lopes, Karoline Neumann Gomes, Jonathan Grassi, Luiz Claudio Barreto Silva Neto, Julia Anhoque Cavalcanti Marcarini, Katia Cirlene Gomes Viana, Luís Carlos Lopes-Júnior.
Formal analysis: Wesley Rocha Grippa, Luís Carlos Lopes-Júnior.
Funding acquisition: Luís Carlos Lopes-Júnior.
Investigation: Luís Carlos Lopes-Júnior.
Methodology: Luís Carlos Lopes-Júnior.
Project administration: Luís Carlos Lopes-Júnior.
Resources: Luís Carlos Lopes-Júnior.
Software: Luís Carlos Lopes-Júnior.
Supervision: Karolini Zuqui Nunes, Luís Carlos Lopes-Júnior.
Validation: Karolini Zuqui Nunes, Wesley Rocha Grippa, Andressa Bolsoni Lopes, Karoline Neumann Gomes, Jonathan Grassi, Luiz Claudio Barreto Silva Neto, Julia Anhoque Cavalcanti Marcarini, Samantha Moreira Felonta, Katia Cirlene Gomes Viana, Luís Carlos Lopes-Júnior.
Visualization: Karolini Zuqui Nunes, Wesley Rocha Grippa, Andressa Bolsoni Lopes, Karoline Neumann Gomes, Jonathan Grassi, Luiz Claudio Barreto Silva Neto, Julia Anhoque Cavalcanti Marcarini, Samantha Moreira Felonta, Katia Cirlene Gomes Viana, Luís Carlos Lopes-Júnior.
Writing – original draft: Karolini Zuqui Nunes, Wesley Rocha Grippa, Andressa Bolsoni Lopes, Karoline Neumann Gomes, Jonathan Grassi, Luiz Claudio Barreto Silva Neto, Julia Anhoque Cavalcanti Marcarini, Samantha Moreira Felonta, Katia Cirlene Gomes Viana, Luís Carlos Lopes-Júnior.
Writing – review & editing: Wesley Rocha Grippa, Andressa Bolsoni Lopes, Karoline Neumann Gomes, Jonathan Grassi, Luiz Claudio Barreto Silva Neto, Julia Anhoque Cavalcanti Marcarini, Samantha Moreira Felonta, Katia Cirlene Gomes Viana, Luís Carlos Lopes-Júnior.

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