

# Symptom Cluster and the Impact on the Global Health Quality of Patients with Advanced Cancer

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*Cluster de Sintomas e o Impacto na Qualidade de Saúde Global de Pacientes com Câncer Avançado*  
Grupo de Síntomas y el Impacto en la Calidad Global de la Salud de los Pacientes con Cáncer Avanzado

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## ABSTRACT

**Introduction:** Patients with cancer can present multiple symptoms that are interrelated, forming the so-called clusters or groups of symptoms. **Objective:** To evaluate the relationship between a cluster of symptoms and the global quality of life of patients with advanced cancer. **Method:** Analytical, cross-sectional study with 146 patients. Sociodemographic characterization and quality of life assessment instruments were used. For data analysis, the Kolmogorov-Smirnov, Mann-Whitney, and Kruskal-Wallis tests were applied. Data collection was carried out between July 2019 and February 2020 and the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30), version 3, was adopted. **Results:** Spearman's correlation was positive between the final score of the symptom scale and the final score of the global health assessment ( $\rho=0.605$ ;  $p<0.001$ ). In addition, it was observed that the increase of 1 point in the question "Did you need to rest?" was associated with an increase of 5.87 points in the global health quality score ( $p<0.01$ ), for the question "Did you feel tired?", 6.14 points ( $p<0.01$ ) and "Did you have shortness of breath?", 5.08 points ( $p<0.01$ ). **Conclusion:** There is a positive correlation between the cluster of symptoms formed by pain, fatigue, dyspnea, nausea, vomiting, insomnia, lack of appetite, constipation, diarrhea and the overall health quality of patients with cancer.

**Key words:** Neoplasms; Quality of Life; Sickness Impact Profile; Signs and Symptoms.

## RESUMO

**Introdução:** Os pacientes com câncer podem apresentar múltiplos sintomas que se inter-relacionam, formando os chamados *clusters* ou agrupamentos de sintomas. **Objetivo:** Avaliar a relação entre um *cluster* de sintomas e a qualidade de saúde global de pacientes com câncer avançado. **Método:** Estudo analítico, transversal, com 146 pacientes. Foram utilizados instrumentos de caracterização sociodemográfica e de avaliação de qualidade de vida. Para análise dos dados, aplicaram-se os testes *Kolmogorov-Smirnov*, *Mann-Whitney* e *Kruskal-Wallis*. A coleta de dados foi realizada entre julho de 2019 e fevereiro de 2020 e utilizado o questionário 30-item *European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire* (EORTC QLQ-C30), versão 3. **Resultados:** A correlação de *Spearman* mostrou-se positiva entre o escore final da escala de sintomas e o escore final da avaliação global da saúde ( $\rho=0,605$ ;  $p<0,001$ ). Além disso, observou-se que o incremento de 1 ponto na pergunta: "Precisou descansar?" associou-se com aumento de 5,87 pontos no escore da qualidade da saúde global ( $p<0,01$ ); para a pergunta "Sentiu-se cansado/a?", 6,14 pontos ( $p<0,01$ ); e "Teve falta de ar?", 5,08 pontos ( $p<0,01$ ). **Conclusão:** Existe uma correlação positiva entre o *cluster* de sintomas composto por dor, fadiga, dispnéia, náusea, vômito, insônia, inapetência, constipação, diarreia e a qualidade de saúde global de pacientes com câncer.

**Palavras-chave:** Neoplasias; Qualidade de Vida; Perfil de Impacto da Doença; Sinais e Sintomas.

## RESUMEN

**Introducción:** Los pacientes con cáncer pueden presentar múltiples síntomas que están interrelacionados, formando los llamados grupos o grupos de síntomas. **Objetivo:** Evaluar la relación entre uno grupo de síntomas y la calidad de vida general de los pacientes con cáncer avanzado. **Método:** Estudio analítico, transversal, con 146 pacientes. Se utilizaron instrumentos de caracterización sociodemográfica y de evaluación de la calidad de vida. Para el análisis de datos, se aplicaron las pruebas de *Kolmogorov-Smirnov*, *Mann-Whitney* y *Kruskal-Wallis*. La recolección de datos se llevó a cabo entre julio de 2019 y febrero de 2020 y se utilizó el cuestionario de calidad de vida básica de la Organización Europea para la Investigación y el Tratamiento del Cáncer (EORTC QLQ-C30), versión 3. **Resultados:** La correlación de *Spearman* fue positiva entre el puntaje final de la escala de síntomas y el puntaje final de la evaluación de salud global ( $\rho=0,605$ ;  $p<0,001$ ). Además, se observó que el aumento de 1 punto en la pregunta "¿Necesitabas descansar?" se asoció con un aumento de 5,87 puntos en el puntaje de calidad de salud global ( $p<0,01$ ); para la pregunta "¿Se sintió cansado/a?", 6,14 puntos ( $p<0,01$ ); y "¿Tuvo dificultad para respirar?", 5,08 puntos ( $p<0,01$ ). **Conclusión:** Existe una correlación positiva entre el conjunto de síntomas compuestos por dolor, fatiga, disnea, náuseas, vómitos, insomnio, falta de apetito, estreñimiento, diarrea y la calidad de salud general de los pacientes con cáncer.

**Palabras clave:** Neoplasias; Calidad de Vida; Perfil de Impacto de Enfermedad; Signos y Síntomas.

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## INTRODUCTION

Cancer is one of the main four causes of early death (before 70 years of age) in most of the countries, it is the leading public health problem in the world. According to the most recent world estimate, 18 million new cases of cancer (17 million without non-melanoma skin cancer) and 9.6 million deaths (9.5 million, excluding non-melanoma skin cancers)<sup>1</sup> occurred.

The National Cancer Institute José Alencar Gomes da Silva (INCA) estimates 625 thousand new cases of cancer (450 thousand, excluding non-melanoma skin cancer) in Brazil for each year of the triennium 2020-2022. Non-melanoma skin cancer will be the most incident (177 thousand) followed by breast and prostate cancer (66 thousand each), colon and rectum (41 thousand), lung (30 thousand) and stomach (21 thousand)<sup>2</sup>. The patients with cancer can present multiple inter-related symptoms, forming clusters or groups of symptoms<sup>3</sup>. These symptoms do not necessarily share the same etiology and can be defined when two or more symptoms are concurrent without necessarily relating to other groups. Therefore, the relation among symptoms of the same group is stronger than the relation with different groups<sup>4</sup>. Different symptoms can occur concurrently or influence each other. The elucidation of these factors helps to enhance the understanding of the physiology and treatment, eventually achieving better management and control for improved quality of life (QoL)<sup>5</sup>.

In case of advanced disease, it can evolve to impossibility of cure with barely controllable signs and symptoms such as fatigue, depression, anxiety, constipation, pain, nausea, vomits, anorexia among others. In this sense, the treatment offered to the patient is palliative instead of curative as these episodes may be related to treatment adverse events or tumor invasion and both cause distress to the patient and negative impact in its QoL<sup>6</sup>.

Consequently, palliative care is meant to improve the QoL of the patient with interventions to alleviate physical, psychological, social and spiritual symptoms<sup>7</sup>. These aspects need attention of the health professional because of the negative impacts concurrent to the endless fight against advanced cancer that can affect the QoL if left untreated<sup>8</sup>.

There are nearly seven thousand palliative care services in more than 90 countries. Of these, only 40 specialized services of this therapeutic modality exist in Brazil<sup>9</sup>.

A study conducted in a São Paulo university indicates a potential educational deficit of health professionals in regard to terminality in Brazil. It is necessary a change of mentality of the professionals who are not always available and willing to adhere to a new organization and in the specialized schools which emphasize technical over

humanistic formation, the latter, a requirement to care for these patients<sup>10</sup>.

According to the World Health Organization Quality of Life Assessment (WHOQOL)<sup>11</sup>, QoL is defined as the individual's perception of its position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. All these aspects address how the individual will achieve its goals, fulfilling its dreams and meetings its expectations, therefore, QoL is considered subjective, reflecting the patient's satisfaction with the evolution of its life. Not only this, a collaborative multicenter project conducted by WHO<sup>12</sup> showed that, in addition to the subjectivity, there is also the multidimension which includes the physical, psychological, social and spiritual aspects and a daily living bipolarity with positive and negative influences impacting the QoL.

The objective of the study was to evaluate the relation of the symptom cluster and the global quality of life of patients with advanced cancer.

## METHOD

Analytical, cross-sectional, quantitative study conducted in a medium-size non-profit hospital with 150 beds in the Municipality of Macaé (RJ), Brazil for patients of SUS cost-free and for private insured patients.

The study population consisted of oncologic patients in treatment at the hospital according to inclusion criteria: patients with cancer stage III or IV, 18 years of age or older, lucid, conscious, able to respond to the items proposed for the study. The exclusion criteria were patients unable to keep oral and/or written communication.

The sample was formed by 35 patients considering level of significance of  $p < 0.05$ , with error type I (alpha) expected of 5%, standard normal variable (Z) associated with level of confidence of 95% equivalent to 1.96 in a population of 160 patients in treatment at the hospital of the study, standard-deviation (SD) of  $\pm 15$  patients for all the variables.

To determine the simple random sample the following formula was utilized:

$$n = 1.96^2 \frac{\sigma^2}{\varepsilon^2}$$

Where:

- n = size of the sample
- $\sigma$  = standard deviation
- $\varepsilon$  = error

The data were collected from July 2019 to February 2020 through interviews, utilizing the 30-items European

Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30), version 3. This collection instrument was produced by the European Organization for Research and Treatment of Cancer for academic use to evaluate the QoL of patients with cancer. The applicability of the questionnaire was validated and is being utilized in several studies in Brazil. The EORTC QLQ-C30 has a score of 0-100, as high the score, worse is the QoL.

The 30-items instrument is divided in five functional scales (physical, role, cognitive, social and emotional function), three symptoms scales (fatigue, pain, nausea and vomiting), one scale evaluating the QoL in general, five single terms (dyspnea, sleep disorder, loss of appetite, constipation and diarrhea) and one isolate item evaluating the financial impact. The responses will be given in a 4-points Likert-type scale, except the items evaluating QoL in general (items 29 and 30) that utilize the 7-points Likert-type scale.

The data were analyzed with the software Statistical Package for the Social Sciences (SPSS), version 21. To characterize the individuals evaluated, the continuous variables were described by mean and SD. The variables were tested through the Kolmogorov-Smirnov test to evaluate whether the data presented normal distribution.

To evaluate the correlation between the global quality of life and the score of the symptoms scale, the Spearman correlation coefficient was utilized as the sample's distribution was not normal. The classification of the correlation coefficient was utilized: correlation coefficient  $<0.4$  (weak magnitude),  $>0.4$  to  $<0.5$  (moderate magnitude) and  $>0.5$  (strong magnitude)<sup>13</sup>.

The linear regression analysis was performed to estimate the association between the dependent variable (global quality of life) and the scale of symptoms, the 13 questions of the score of the scale of the symptoms were included in the models and those with  $p$ -value $<0.05$  were kept in the final model.

The Institutional Review Board of the Psychiatry Institute of the Federal University of Rio de Janeiro (UFRJ) approved the study in compliance with the requirements of the National Health Council related to the rules for clinical trials with human subjects according with Resolution 466/2012, Report number 2.821.570.

## RESULTS

Of the patients with cancer who joined the study ( $n=146$ ), 140 (96%) provided complete data about symptoms and global quality of life. The final mean score of the symptoms scale was 34.7 (SD=26.2) and 32.3 (SD=25) for the global health quality score.

The mean age of the patients was 60 years ( $\pm 16.65$ ), being 57.83% females, 35.29% Whites and 64.71% Blacks or Browns (Table 1). The patients were treated/ followed-up by SUS.

**Table 1.** Sociodemographic data of patients and types of cancer. Macaé, RJ, Brazil, 2020

<b>Gender</b>	Female	57.83%
	Male	42.17%
<b>Age</b>	80 years or more	10.74%
	70-79	18.91%
	60-69	32.37%
	50-59	13.46%
	40-49	10.74%
	30-39	8.16%
	20-29	5.44%
<b>Color</b>	Whites	35.29%
	Blacks or Browns	64.71%
<b>Types of cancer</b>	Breast	35.86%
	Colorectal	20.51%
	Prostate	10.1%
	Stomach	7.74%
	Lung	7.74%
	Others	17.93%

Among the 13 questions of the score of symptoms, more than 60% of the interviewees responded “no” to four outstanding symptoms: diarrhea (83.6%), vomit (73.6%), shortness of breath (67.9%) and nausea (60.7%). More than 20% of the interviewees responded “very much” to the symptoms: “needed to rest” (28.6%), “pains disturbed the daily activities” (25.7%), “pains” (26.4%), “felt weak” (24.3%) and “felt tired” (20%) (Table 2).

For the two questions addressing the score of global health quality with evaluations ranging from 1 (very bad) to 7 (excellent) points, the final mean was 3 (SD=1.6) for the question “How would you score your health in general in the last week?” and 2.87 (SD=1.6) for “How would you score your global quality of life during the last week?”. 84.3% of the interviewees scored  $\leq 4$  for both questions.

The Spearman correlation showed there is a strong and positive correlation between the final score of the scale of symptoms and the final score of the global health assessment ( $\rho=0.605$ ;  $p<0.001$ ).

A multiple linear regression model was developed to evaluate the association between the symptoms reported by the patients with cancer and global health quality. The final model for global health quality included three questions for the symptoms score: “Did you need to rest?”, “Did you feel tired?” and “Did you have shortness of breath?”. The increase of 1 point in the question “Did

**Table 2.** Questions addressing the score of symptoms, n=140. Macaé, RJ, Brazil, 2020

Questions	Mean score (SD)	Symptoms scale n (%)			
		No (1 point)	A little (2 points)	Very much (3 points)	Severe (4 points)
Did you need to rest?	2.33 (1.2)	44 (31.4)	46 (32.9)	10 (7.1)	40 (28.6)
Did you feel weak?	2.17 (1.2)	58 (41.4)	34 (24.3)	14 (10)	34 (24.3)
Did you feel tired?	2.12 (1.1)	58 (41.4)	35 (25)	19 (13.6)	28 (20)
Did you have nausea?	1.75 (1.0)	85 (60.7)	25 (17.9)	10 (7.1)	20 (14.3)
Did you vomit?	1.51 (0.9)	103 (73.6)	19 (13.6)	2 (1.4)	16 (11.4)
Did you have pains?	2.24 (1.2)	54 (38.6)	35 (25)	14 (10)	37 (26.4)
Have the pains disturbed your daily activities?	1.14 (1.2)	67 (47.9)	23 (16.4)	14 (10)	36 (25.7)
Did you have shortness of breath?	1.64 (1.0)	95 (67.9)	19 (13.6)	8 (5.7)	18 (12.9)
Did you have difficulties to sleep?	1.93 (1.1)	72 (51.4)	28 (20)	18 (12.9)	22 (15.7)
Have you lost the appetite?	1.86 (1.1)	82 (58.6)	21 (15)	12 (8.6)	25 (17.9)
Did you have constipation?	1.81 (1.1)	83 (59.3)	20 (14.3)	17 (12.1)	20 (14.3)
Did you have diarrhea?	1.29 (0.7)	117 (83.6)	12 (8.6)	4 (2.9)	7 (5)
Have your physical condition or medical treatment caused financial problems?	1.83 (1.0)	75 (53.6)	31 (22.1)	17 (12.1)	17 (12.1)

you need to rest?” was associated with the increase of 5.87 points in the score of the global health quality ( $p<0.01$ ); for the question “Did you feel tired?”, the increase was 6.14 points ( $p<0.01$ ); for “Did you have shortness of breath?”, the increase was 5.08 points ( $p<0.01$ ) (Table 3).

**Table 3.** Association among the symptoms reported and the quality of health of patients with cancer (n=140) evaluated in the multiple linear regression models. Macaé, RJ, Brazil, 2020

	Quality of Global Health*	
	Regression Coefficient (CI 95%)	p-value
Did you need to rest?	5.87 (2.07; 9.68)	<0.01
Did you feel tired?	6.14 (2.09; 10.2)	<0.01
Did you have shortness of breath?	5.08 (1.32; 8.83)	<0.01

(\*) Estimated by EORTC QLQ-C30<sup>14</sup>.

## DISCUSSION

The evaluation of the clusters is a tool that helps to diminish the inaccuracies due to non-grouped assessment of the symptoms. Therefore, the recognition

of the importance of the grouping can change clinical practice and allow the improvement of the interventions, interfering directly in the care to the patient. The present study presented statistical evidences of strong positive correlation between a symptoms cluster and the global health of patients with advanced cancer.

The patient with advanced cancer experiences a group of symptoms which damages intensely its well-being. Staging is a roman numeral from I (1) to IV (4) for the majority of the cancers. Stage I cancers are less advanced and typically have better prognosis. Cancers at higher advanced stages are worrying as metastases and may demand stronger treatment. Some types of cancers are classified as stage 0, meaning that it is still located in the layer of cells where it began and did not spread<sup>15</sup>.

As stages III and IV of cancer are the most advanced, their treatment is quite complex and palliative care is a great ally. Thus, palliative care should be provided by a skilled multi-disciplinary team to tackle with fears, sufferings and anguishes of the patient and its family, knowing how to act in face of the human finitude and the patient's needs<sup>16</sup>.

Aligned with this concept, as great the number of symptoms reported by a patient in palliative care,

poorer will be its QoL and the most recurrent symptoms clusters are pain, fatigue, loss of appetite, constipation, pallor, cachexia, dyspnea, poor sleep quality, dysphagia, depression, dysgeusia, low nutritional status, feeling of dependence and lack of social and family support<sup>17</sup>.

Among the symptoms mentioned, oncologic pain is reported in 70% to 90% of the advanced cases characterized as a severe symptom and one of the most reported by patients<sup>18</sup>. Brazil is the country with the highest rate of complaints of oncologic pain in Latin America affecting from 25% to 30% of the patients in the initial phase, 50% in several stages of cancer and from 70% to 90% of those in advanced stage<sup>19</sup>. In this sense, pain relief is one of the main objectives of palliative care since it causes suffering and even impairment of daily activities; health professionals assigned to manage the pain are challenged since pain is a subjective symptom that occurs when the patient claims it has and exists and when it says it exists. It requires health professional capability for treatment efficacy<sup>20</sup>.

Of the cluster created in the present study, three symptoms stood out during data collection: tiredness, fatigue, and dyspnea. The score of global health quality augmented when the responses to these symptoms increased one point, showing the necessity of attention to these items.

Aware that symptoms clusters are defined as groups of at least two or three simultaneous symptoms related among each other<sup>21</sup>, the Brazilian nurses conducted a systematic review and pointed out that the symptoms grouped most encountered are neuropsychological and gastrointestinal<sup>22</sup>.

An American study noticed that pain, dyspnea, fatigue, and emotional stress onset simultaneously and are interdependent, therefore, are inter-related among one another since they can produce cumulative effect<sup>23</sup>. In another Brazilian study, the EORTC QLQ-C30 scale of symptoms was utilized where pain, fatigue, insomnia, and loss of appetite stood out jointly<sup>24</sup>.

Poor quality sleep was present in nearly 75% of the study participants, corroborating the national and international literature where the authors warned about sleep disorders for the individual with cancer<sup>25</sup>. For the patients with poor sleeping quality, sleep disorders formed clusters with the symptoms of concern and sadness.

A study about grouping of patients with lung cancer analyzed the clusters and considered the magnitude of the symptoms of high prevalence according to the EORTC QLQ-C30 scale of symptoms; these symptoms were fatigue, pain, dyspnea, and insomnia. Among the results, three groups (subgroups) of patients were identified, based in the magnitude of the four most

prevalent symptoms. The three subgroups of patients were: patients with mild symptoms (n=30; 60%); patients with moderate symptoms (n=14; 28%) and patients with severe symptoms (n=6; 12%). The subgroup of patients with severe symptoms had the worst QoL as measured through the total scores and the integrated dimensions of the three instruments<sup>26</sup>.

In the cluster formed in the current study, fatigue and tiredness were found. Fatigue can be described as a symptom of unbalance between the state of rest and activity, which causes physical and mental weariness, but the individual reporting it, recovers if the cause ceases to exist<sup>27</sup>. Cancer related fatigue (CRF) is different than this condition because there is no symptom relief with sleep/rest and for this, it is considered a factor that diminishes the QoL and consequently, the individual satisfaction. Patients in oncologic treatment, mainly those submitted to chemotherapy (CT) show persistence of the symptom after the end of the treatment and recovery of the disease too. The prolongation of the fatigue defines it as chronic and implies in the possibility of a metabolic and physiologic adaptation as deconditioning and cachexia, for instance<sup>28</sup>.

Many patients with cancer develop anemia as consequence of its malignant disease, treatment or even comorbidities previously onset. Anemia is one of the leading reversible causes of CRF<sup>29</sup>, present in more than 40% of the cases and in patients during CT, the incidence can reach until 90%<sup>30</sup>.

Another symptom which stood out in this study was dyspnea. It may correlate with the reduction of the levels of hemoglobin, which negatively impacts survivorship and emphasizes CRF<sup>31</sup>. The term dyspnea is utilized to define a subjective feeling of shortness of breath or breathing difficulty the ill individual claims it feels, being one of the most prevalent symptoms in several studies, occurring between 19% and 51% of the oncologic ill and augments rapidly with the disease progression and in the end of the life, especially in patients with lung cancer<sup>32</sup>.

The limitations of this study like the convenience sample and the relatively small sample because it was conducted in a countryside town of the state of Rio de Janeiro, hampered the analysis of the effect of symptoms cluster about the quality of the global health of patients with cancer, considering the influence of other variables as gender, age, education. Therefore, it is suggested that new studies are conducted in order to evaluate the impact on the global health of patients with cancer and the possible modification of the effects while considering other symptoms clusters.

To care for a patient with advanced cancer and many times without possibility of current cure, it is necessary

to adopt a multi-disciplinary and even inter-disciplinary perspective. In its essence, the palliative care team is multi-disciplinary. This condition arises from the heterogeneity of the individual needs of patients and their families. In this context, no professional formation is wide enough to address all the aspects needing attention<sup>33</sup>. Therefore, to reach the quality of global health it is necessary to reflect about full care in order to meet all the dimensions, that is, bio-psychosocial and spiritual.

## CONCLUSION

The present study conducted in a countryside city of the State of Rio de Janeiro showed there is a strong positive correlation between the cluster of symptoms formed by pain, fatigue, dyspnea, nausea, vomit, insomnia, inappetence, constipation, diarrhea, and quality of global health of patients with advanced cancer. Therefore, it is suggested the applicability in other settings of the country as, for instance, in great urban centers.

## CONTRIBUTIONS

All the authors contributed for the study conception and design, collection, analysis, and interpretation of the data, wording, critical review and approved the final version to be published.

## DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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