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Assessment of symptom intensity in patients with stage III and IV cancer

Avaliação da intensidade dos sintomas em pacientes com câncer em estadiamento III e IV

Evaluación de la intensidad de los síntomas en pacientes con cáncer en estadios III y IV

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ABSTRACT

Objective: to evaluate the intensity of symptoms in patients with advanced cancer. **Method**: a quantitative, descriptive, longitudinal study was conducted at a university hospital in southern Brazil, including patients with advanced cancer. Initially, sociodemographic and clinical profiles were identified. During follow-up, symptoms were assessed weekly using the Edmonton Symptom Assessment System. **Results**: the 23 participants had a mean age of 53.3 years, 78.3% self-reported female gender, and six were in stage III, while 17 were in stage IV. The most frequent diagnoses were breast (30.8%) and colon and rectal (17.4%) cancer. The symptom with the highest mean intensity was fatigue (5.35%), followed by anxiety (5.14) and dyspnea (4.54). **Conclusion**: symptoms in patients with advanced cancer can manifest simultaneously and, in some cases, in sudden peaks of high intensity. Assessment is essential for effective management and improving the quality of life and survival of these patients.

Descriptors: Neoplasms; Oncology Nursing; Signs and Symptoms; Symptom Assessment; Nursing Assessment.

RESUMO

Objetivo: avaliar a intensidade dos sintomas em pacientes com neoplasias avançadas. **Método:** estudo quantitativo, descritivo, longitudinal, desenvolvido em um hospital universitário no sul do Brasil, incluindo pacientes com neoplasias avançadas. Inicialmente, identificou-se os perfis sociodemográfico e clínico. No seguimento, foram avaliados os sintomas por meio do *Edmonton Symptom Assessment System*, uma vez por semana. **Resultados:** os 23 participantes tinham idade média de 53,3 anos, 78,3% se autodeclararam do sexo feminino e seis encontravam-se no estadiamento III, enquanto 17 no IV. Os diagnósticos mais frequentes foram daqueles com neoplasias de mama (30,8%) e de cólon e reto (17,4%). O sintoma com maior média de intensidade foi fadiga (5,35), seguido de ansiedade (5,14) e dispneia (4,54). **Conclusão:** os sintomas em pacientes com neoplasia avançada podem se manifestar de forma simultânea e, em alguns casos, em picos repentinos de alta intensidade. A avaliação é fundamental para manejo eficaz e melhora da qualidade de vida e sobrevida desses pacientes.

Descritores: Neoplasias; Enfermagem Oncológica; Sinais e Sintomas; Avaliação de Sintomas, Avaliação em Enfermagem.

RESUMEN

Objetivo: evaluar la intensidad de los síntomas en pacientes con neoplasias avanzadas. **Método:** estudio cuantitativo, descriptivo y longitudinal, desarrollado en un hospital universitario en el sur de Brasil, que incluyó pacientes con neoplasias avanzadas. Inicialmente, se identificaron los perfiles sociodemográfico y clínico. Posteriormente, los síntomas fueron evaluados mediante el *Edmonton Symptom Assessment System*, una vez por semana. **Resultados:** los 23 participantes tenían una edad media de 53,3 años, el 78,3% se autodeclaró de sexo femenino, y seis se encontraban en estadio III, mientras que 17 en estadio IV. Los diagnósticos más frecuentes fueron neoplasias de mama (30,8%) y de colon y recto (17,4%). El síntoma con mayor media de intensidad fue la fatiga (5,35), seguido por la ansiedad (5,14) y la disnea (4,54). **Conclusión:** los síntomas en pacientes con neoplasias avanzadas pueden manifestarse de forma simultánea y, en algunos casos, con picos repentinos de alta intensidad. La evaluación es fundamental para un manejo eficaz y para la mejora de la calidad de vida y la sobrevida de estos pacientes.

Descriptores: Neoplasias; Enfermería Oncológica; Signos y Síntomas; Evaluación de Síntomas; Evaluación en Enfermería.

INTRODUCTION

Malignant neoplasms are classified as advanced from stage III onwards due to the significant size of the tumor or proximity to a vital organ. Stage IV, or metastatic, occurs when neoplastic cells migrate through metastasis to other tissues, either near or distant from the primary site. To determine neoplasm staging, the tumor-node-metastasis (TNM) system is used, which indicates the size of the primary tumor and extent of the disease (T), the presence of lymph nodes (N), and the presence of metastasis near or distant from the primary site (M)[1,2].

An important parameter for the diagnosis of malignant neoplasms is histopathological analysis, also called anatomopathological examination, considered the gold standard for diagnostic confirmation and essential for prognostic assessment and therapeutic targeting. This examination evaluates the tissue composition of the tumor in

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comparison with normal tissue, determining the histological grade. Histological grade categorization includes grade I (well-differentiated), grade II (moderately differentiated), grade III (poorly differentiated), and grade IV (undifferentiated or anaplastic)[2].

The level of aggressiveness of the neoplasm is related to the histological grade and, associated with the individual's sociodemographic factors, influences the intensity of the symptoms presented.[3] Increased symptom intensity is an important predictor of patients' quality of life because it directly interferes with their daily activities[4,5].

Advanced neoplasia offers a low prospect of cure or complete remission, causing suffering to the patient and family.[6] Patient care is considered complex due to the high burden of distressing symptoms triggered by the disease, including pain, nausea, dyspnea, fatigue, loss of appetite, drowsiness, anxiety, and depression[7]. The approach aims to minimize discomfort, promoting physical and emotional well-being[8].

Some of the most intense physical symptoms reported by cancer patients are pain, fatigue, dyspnea, nausea, vomiting, insomnia, loss of appetite, constipation, and diarrhea[9]. However, the prevalence of psychological symptoms is also significant, with anxiety and depression ranging from 20% to 25%[4].

Symptom relief is a priority in comprehensive health care and is assessed primarily through self-reporting by the patient experiencing the symptoms.[5] Therefore, palliative care (PC) should be recommended early, concomitantly with disease-modifying treatment, which will contribute to an accurate assessment of symptoms resulting from disease progression[10].

Given the need for effective symptom management that provides relief and comfort to patients with advanced cancer, assessment becomes a fundamental step in care planning. To systematically assess the symptoms presented by these patients, it is necessary to use appropriate instruments, such as the Edmonton Symptom Assessment System (ESAS-r) tool[11,12]. The ESAS-r is a multisymptom assessment tool widely recommended in oncology palliative care, translated into more than 20 languages, and validated in several countries, including Brazil[13,14].

This study aimed to assess the intensity of symptoms presented by patients with stage III and IV cancers.

METHOD

This is a quantitative, observational, descriptive, and longitudinal study. Data were reported in accordance with the recommendations of the Strengthening the Reporting of Studies in Epidemiology (STROBE) statement.

Participants were patients treated by the oncology department of a university hospital in southern Brazil, with a confirmed diagnosis of any type of neoplasm, age 18 years or older, preserved oral communication, and cognitive ability to understand the ESAS-r mechanism. Recruitment was based on convenience, during outpatient care or in the inpatient unit, still during the global health emergency caused by COVID-19. The Diversity, Equity, Inclusion, and Accessibility (DEIA) principles for scientific research were observed, and their applicability was rigorously assessed at all stages of the study, including the development of the Sociodemographic and Clinical Profile.

Data collection took place between February and July 2022. Three instruments were used, the first being a Sociodemographic and Clinical Profile questionnaire, developed by the researchers. The second instrument was the Palliative Performance Scale (PPS), a tool capable of quickly and conveniently assessing the patient's functional and cognitive profile, in addition to guiding prognosis.[15] In this study, the PPS was used in two phases: the first to assess the participant's oral communication skills and understanding of the ESAS-r, and the second to assess their level of consciousness during the end-of-life period.

The third instrument was the Edmonton Symptom Assessment System (ESAS-r), a Likert-type symptom assessment scale with scores ranging from zero (representing the absence of the symptom) to 10 (representing the highest possible intensity), according to the level of symptom intensity at the time of assessment. The ESAS-r is structured to assess nine symptoms, in addition to an open-ended question for the patient to report another symptom or problem.[14,16]

Participants had their symptoms assessed using the ESAS-r during weekly follow-up. The initial assessment (D1 – First day of assessment) was conducted in person. Follow-up assessments (D2 to DX – Days of symptom assessment follow-up) took place in the institution's oncology department, on the day of consultations (with a physician or multidisciplinary team), in the inpatient units, and via telemonitoring. Telemonitoring was conducted via landline or mobile phone and via WhatsApp® video call, according to the participant's choice, lasting approximately five minutes. The date and time for follow-up assessments were chosen by the participants. During

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data collection on hospital premises, the presence of a family member or caregiver in a private setting was guaranteed, if the participant so desired.

Data were analyzed using GraphPad Prism 5.0 software. For statistical analysis of ESAS-r symptoms, two-way analysis of variance (ANOVA) was applied, with $p<0.05$ considered statistically significant[17]. The graphical representation shows the variations in responses to a single symptom over the weeks of evaluation and the differences in intensity among all symptoms assessed.

The study was approved by the Research Ethics Committee of the institution where the study was conducted. Participants were instructed on the ethical aspects of scientific research and, upon acceptance, signed an informed consent form (ICF). To protect their identity and ensure anonymity, a coding system was adopted.

RESULTS

A total of 247 participant assessments were conducted using the ESAS-r. The average age of participants was 53.3 years; 78.3% self-identified as female; 78.3% had completed elementary or high school; 56.5% self-identified as Catholic and 43.5% Protestant; 78.3% self-identified as White; 52.2% married and 30.5% single. Regarding nationality, 91.4% were from the southern region of Brazil. For 82.7% of participants, the primary caregiver was a family member, and 17.3% reported having no primary caregiver.

Regarding lifestyle habits, 43.5% of participants reported frequent alcohol consumption between 10 and 51 years throughout their lives. And 26% used tobacco for a period of ten to 30 years, with a daily amount of 20 to 40 filtered cigarettes.

Table 1 shows how the evaluations were followed, where W+1 corresponds to the first week of evaluation, followed by W+n, where "n" is the number of weeks the participant was evaluated. The longest follow-up period was W_{+18}.

Table 1: Weeks of follow-up per participant. Curitiba, PR, Brazil, 2022.

Follow-up assessments	
Participant	**Weeks**
P1	$W_{+1} – W_{+7}$
P2*	$W_{+1} – W_{+16}$
P3*	$W_{+1} – W_{+11}$
P4	$W_{+1} – W_{+15}$
P5	$W_{+1} – W_{+9}$
P6*	$W_{+1} – W_{+7}$
P7	$W_{+1} – W_{+18}$
P8	$W_{+1} – W_{+11}$
P9	$W_{+1} – W_{+10}$
P10	$W_{+1} – W_{+18}$
P11	$W_{+1} – W_{+14}$
P12	$W_{+1} – W_{+11}$
P13	$W_{+1} – W_{+14}$
P14	$W_{+1} – W_{+14}$
P15	$W_{+1} – W_{+13}$
P16	$W_{+1} – W_{+10}$
P17	$W_{+1} – W_{+10}$
P18	$W_{+1} – W_{+10}$
P19	$W_{+1} – W_{+10}$
P20	$W_{+1} – W_{+7}$
P21	$W_{+1} – W_{+7}$
P22	$W_{+1} – W_{+7}$
P23	$W_{+1} – W_{+6}$

Note: *Discontinuation of participants due to death

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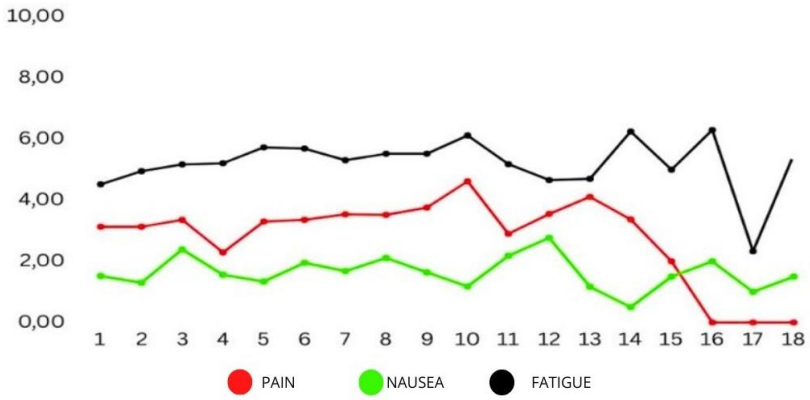
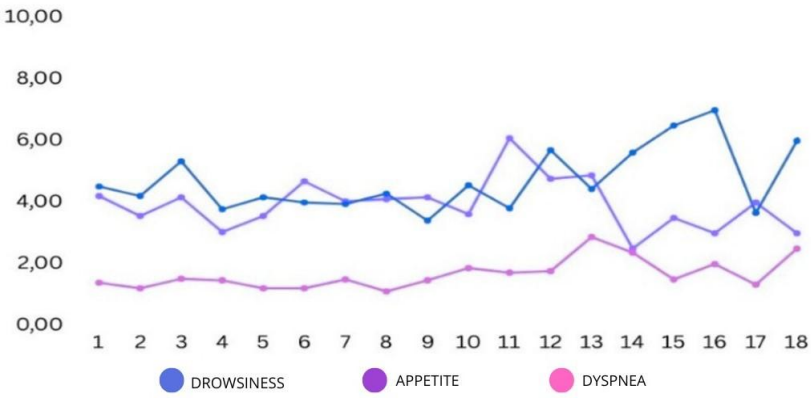
In six assessments, three participants hospitalized near the end of life did not have the cognitive capacity to understand and respond to the ESAS-r. In these cases, the PPS was applied, resulting in a score of 10% in the "Level of Consciousness" dimension, indicating "confusion or coma." Therefore, the assessment was performed by the inpatient unit nurse who completed the ESAS-r items, assessing the participant's symptoms, as recommended by the ESAS - Revised Administration Manual[18].

In W+1, 73.9% of participants had stage IV neoplasia with metastatic disease, and 26.1% had stage III neoplasia. The diagnoses presented were: breast cancer (30.8%), colon and rectal adenocarcinoma (17.4%), squamous cell carcinoma (SCC) of the cervix (13%), prostate adenocarcinoma and Hodgkin's lymphoma (8.7%), large B-cell lymphoma (4.3%), ovarian cancer (borderline tumor) (4.3%), type I cholangiocarcinoma (4.3%), nasopharyngeal carcinoma (4.3%), and small cell lung carcinoma (4.3%). Throughout the treatment, 100% of the participants underwent chemotherapy, with radiotherapy being combined in 26%.

Figures 1, 2, and 3 show the evolution of average symptom intensity over the 18 weeks of evaluation.



Notes: The y-axis represents the average score of each symptom presented by the participants; and the x-axis represents the week of evaluation with the ESAS-r.
Figure 1: Evolution of the average intensity of pain, nausea, and fatigue over the 18 week evaluated. Curitiba, PR, Brazil, 2022.



Notes: The y-axis represents the average score of each symptom presented by the participants; and the x-axis represents the week of evaluation with the ESAS-r.
Figure 2: Evolution of the average intensity of sleepiness, appetite, and dyspnea over the 18 weeks evaluated. Curitiba, PR, Brazil, 2022.

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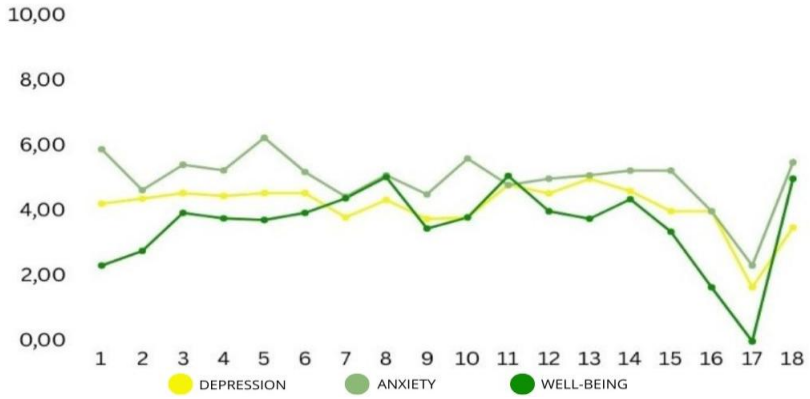

Notes: The y-axis represents the average score of each symptom presented by the participants; and the x-axis represents the week of evaluation with the ESAS-r.
Figure 1: Evolution of the average intensity of depression, anxiety, and well-being over the 18 weeks evaluated. Curitiba, PR, Brazil, 2022.

Table 2 presents variables of intensity of manifestation for each symptom.

Table 2: Descriptive data on the intensity of symptoms. Curitiba, PR, Brazil, 2022.

Item evaluated	Mean	Median	Mode	Interquartile Ranges (Q1-Q3)
Fatigue	5,35	5,0	5,0	3,0 – 8,0
Anxiety	5,12	5,0	8,0	2,0 – 8,0
Dyspnea	4,54	0,0	0,0	0,0 – 3,0
Drowsiness	4,44	5,0	5,0	2,0 – 7,0
Depression	4,36	5,0	0,0	0,0 – 8,0
Appetite	4,07	5,0	0,0	2,0 – 7,0
Well-being	3,77	3,0	0,0	2,0 – 6,0
Pain	3,38	3,0	0,0	0,0 – 5,0
Nausea	1,76	0,0	0,0	0,0 – 3,0

Analysis of variance (ANOVA) indicated statistically significant differences between the mean intensity of the different symptoms ($p<0.05$). The mean values measured for fatigue, 5.35 (±2.72), are the highest among all symptoms.

Medians close to the midpoint of the scale indicate a moderate level of self-reported intensity for most symptoms. Distinct modes suggest variation in reported intensity over the weeks.

Wide interquartile ranges (IQRs) for fatigue and anxiety indicate greater dispersion of scores. Symptoms with a narrower IQR, such as nausea and dyspnea, show more consistent responses.

Regarding emotional symptoms, anxiety was self-reported by 100% of participants, with intensity levels ranging from one to ten. It was the symptom with the second-highest mean among those evaluated, and the higher mode suggests greater variation in the scores presented. Furthermore, 78.3% reported feelings of depression. Drowsiness had the fourth highest mean intensity (4.44), reported by 95.6% of participants.

Pain was present in approximately 70% of the 247 assessments, at varying levels of intensity. Despite the mean of 3.38, self-reported pain was present in 47.8% of the moderate and high intensity assessments. Only 4.3% of participants reported no pain in any of the assessments.

Dyspnea was present in 68% of participants. The reported effective self-management measures for mild dyspnea were: adopting a sitting or semi-sitting position and using home fans ventilating towards the face. During the 18-week assessment, 26% (n=6) of participants showed disease progression, experiencing high-intensity dyspnea peaks (≥7), requiring oxygen supplementation, and half of these participants (n=3) died.

Nausea was less intense on average (1.76). However, there were reports of high intensity peaks (≥7) on a scale of zero to ten.

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In the "other problem" item, constipation was reported in 13.8% of the 247 assessments, affecting 43.5% of participants, and was related to morphine use. The mean constipation intensity was 5.15 (±2.43). Among those who reported this symptom, 90% reported frequent use of laxatives for management, and 10% reported only dietary management.

DISCUSSION

Symptom assessment in patients with advanced cancer should be performed continuously, optimizing symptom perception and interpretation through self-reporting[19]. Symptoms manifest dynamically, and understanding the sociodemographic profile is essential for the assessment process, as these are variables inherent to the individual that impact symptom intensity and the discomfort, they cause[20]. The main symptoms of advanced cancer manifest simultaneously[21].

A study on symptoms in patients with advanced cancer conducted in Rio de Janeiro, Brazil, presents data on sociodemographic and clinical profiles regarding gender, average age, and type of cancer, like those of the present study: average age over 50 years, majority female, and the most prevalent diagnosis was breast cancer[9].

Regarding pain, the results corroborate data from the International Association for the Study of Pain (IASP), which reveal a prevalence of pain in approximately 90% of patients with advanced cancer[22]. However, a meta-analysis of 444 studies published between 2014 and 2021 concluded that pain prevalence and intensity decreased compared to rates published in previous periods. It is suggested that these results are the result of greater attention paid to pain assessment by health services[21].

Opioids are the main class of medications used for pain management, despite the risk of physical and psychological dependence, as well as adverse effects that can trigger or worsen other symptoms, contributing to the manifestation of multiple and concomitant symptoms in cancer[23]. Prolonged use of opioids to manage cancer pain is also a risk factor for depression, affecting 20 to 30% of patients[24].

The results of this study reveal that anxiety and depression affected 100% and 78% of participants, respectively. These rates are higher than those of a study conducted in Beijing, which assessed the emotional symptoms of 176 women with metastatic breast cancer. The incidence of depression, anxiety, and stress was 52.3%, 60.2%, and 36.9%, respectively. Physical symptoms such as pain, dyspnea, and loss of appetite were associated with increased depression[25]. Family members are also affected by these psychological symptoms[10,26].

A quantitative study of 202 cancer patients in northern Brazil established a relationship between anxiety, depression, and stress and QoL. The prevalence of mental illness was found to be 24.76% for depression, 36.63% for anxiety, and 27.23% for stress. There is also a significant relationship with pain, nausea, and dyspnea, which results in a decrease in QoL. 27 In Greece, a study of 150 inpatients and outpatients oncology patients highlights the importance of monitoring the mental health of cancer patients. Improperly managed psychological symptoms affect not only QoL but also treatment adherence and survival. Pain, nausea, dyspnea, and fatigue, when not properly managed, increase levels of anxiety and depression[4].

In a study conducted in Spain, 748 participants with advanced cancer were evaluated. The prevalence of depression was 44.3%. Patients with greater functional capacity and a positive attitude toward coping with the disease presented less intense symptoms of depression[29].

A study conducted in São Paulo, Brazil, with 135 cancer patients treated in PC outpatient clinics used the ESAS-r as one of the instruments for assessing symptoms. The results demonstrated that increased symptom manifestation is related to a decreased perception of spiritual well-being and reduced functionality. The significant rates of anxiety and depression presented by the sample were noteworthy[3|].

Regarding the symptom of appetite, the loss of appetite frequently observed in cancer patients can cause anorexia and weight loss. However, anorexia in cancer represents an important adaptive response, allowing the body to mobilize energy reserves to sustain the increased metabolism needed to curb an immune response and heal injuries or repair the destruction caused by rapidly dividing malignant cells. 31 Loss of appetite in advanced cancer ranges from 30% to 80% for anorexia[32].

A retrospective study of 90 cancer patients conducted in Italy found that one-third of the sample had nutritional deficiencies related to depression[33]. Malnutrition causes approximately 20% of deaths, and it is estimated that 50 to 80% of patients with advanced cancer are malnourished[34].

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According to our results, nausea was among the symptoms evaluated. Nausea has multiple causes, including disease progression, and is not associated solely with chemotherapy and radiotherapy treatments, or with the use of opioids for pain and dyspnea management[35]. Effective nausea management is a key predictor of cancer patients' QOL. A detailed assessment is essential to determine its etiology[36]. A cross-sectional observational study in the United States of 148 women with metastatic breast cancer found that patients who experienced unmanaged pain and nausea during treatment reported higher levels of anxiety and depression.[37]

Our results indicate that fatigue was widespread among participants, corroborating a study conducted at a Japanese university hospital with 608 patients undergoing outpatient antineoplastic chemotherapy. The sample's symptoms were assessed using the Edmonton Symptom Assessment System Revised Japanese version (ESAS-rJ) before and after chemotherapy administration, and a 70.4% prevalence of fatigue was found[38].

Fatigue in cancer patients is characterized as a persistent symptom, a subjective sense of physical, emotional, and cognitive tiredness, or cancer-related exhaustion. 39,40 A study of 146 patients with advanced cancer observed the interrelationship between fatigue and other symptoms such as pain, dyspnea, loss of appetite, anxiety, and nausea. The greater the number of symptoms, the lower the patient's QOL[9].

A study evaluated the nutritional status of 100 patients treated at a hospital in southern Brazil. A significant relationship between protein deficiency and cancer-related fatigue was demonstrated. It was concluded that a high-protein diet, combined with restorative sleep and physical activity, are effective measures for managing fatigue in cancer patients[41].

In a study of 30 end-of-life cancer patients in the Federal District, Brazil, the ESAS-r and PPS tools were used to assess symptoms. The objective was to compare the levels of these symptoms among patients admitted for exclusive PC for 72 hours with their levels at the time of admission. The conclusion was that there was an improvement in symptom management, but with increased levels of fatigue and sleepiness. The importance of continuous symptom assessment was emphasized, confirming the need for training healthcare professionals and promoting the population's access to specialized PC services[13].

Drowsiness was present in 95.6% of the participants in this study. This corroborates an integrative review of cancer PC patients, which identified the symptom as one of the ten most prevalent[42]. An observational study on sleep quality in 120 cancer patients undergoing chemotherapy in northeastern Brazil found that over 70% of the sample had sleep disorders. The effects of chemotherapy can affect sleep for up to five years if not adequately treated[43].

Dyspnea is one of the five main symptoms affecting cancer patients. Caused by a variety of factors, it has a highly debilitating potential and worsens in the last six weeks of life. Its multifactorial origin makes assessment difficult, which hinders management. As the cancer worsens, dyspnea tends to increase, with both pharmacological and non-pharmacological measures recommended[44]. The use of fans aimed at the face is a widely recommended measure and can provide relief from mild to moderate dyspnea in patients with advanced cancer[45].

Terminal dyspnea is defined as dyspnea in patients with an estimated life expectancy of weeks to days, with rapid worsening over days or hours as death approaches[46]. A study of 91 participants nearing the end of life concluded that dyspnea increases over time and self-reporting capacity gradually declines, hindering assessment and effective management[47]. Similarly, participants in this study who experienced significant disease worsening experienced worsening dyspnea, requiring pharmacological support and oxygen supplementation.

Constipation was reported by almost half of the participants in this study at some point during the assessments and was associated with morphine use. These data are consistent with a prospective multicenter study in Italy of 246 participants with advanced cancer, which found a lack of prevention and undertreatment of constipation[48]. The prevalence of constipation in cancer patients using opioids is over two-thirds, and the impacts on QOL are significant[49]. In addition to constipation resulting from decreased peristalsis, symptoms such as nausea, pain, constipation, and drowsiness are also frequently associated with the mechanisms of action of opioids[50].

The results of this study highlight the need for health policies that strengthen palliative care in oncology care. Measures such as training healthcare professionals, prioritizing access to medications and therapies for symptom relief, improving service structures, and incorporating quality indicators to monitor the effectiveness of care are

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essential to prioritize comprehensive care for the needs of patients with advanced cancer, focusing on the individual's quality of life and the dignity that symptom relief provides[51].

Study limitations

The reduced demand for outpatient care due to social distancing measures during the COVID-19 pandemic and the need to include different cancer types to increase the number of participants may have limited the ability to obtain a representative sample.

The Palliative Performance Scale was applied as a complementary tool in the development of this study. Although widely used in palliative care, studies that provide psychometric evidence tend to support the use of the tool in the Brazilian context.

Studies are still needed to strengthen and consolidate the symptom assessment process in patients with advanced cancer. Implementing methodologies focused on individual cancer types will contribute to deepening specific knowledge and improving the systematic assessment process, tailored to the multidimensional and distinct needs of each group.

CONCLUSION

The results showed that the most intense symptoms reported by participants were fatigue and anxiety. It was observed that symptoms in patients with advanced cancer can manifest simultaneously and, in some cases, present sudden peaks of high intensity. This finding reinforces the importance of continuous and systematic symptom assessment for patients with advanced cancer.

The use of validated instruments such as the ESAS-r for rigorous monitoring of symptom manifestations contributes to care planning, favoring effective symptom management and improving the quality of life and survival of these patients.

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Use of artificial intelligence tools

Authors declare that no artificial intelligence tools were used in the composition of the manuscript "*Assessment of symptom intensity in patients with stage III and IV cancer*".