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Identifying symptom clusters in adults with gastrointestinal, breast, uterine, and ovarian advanced cancers in Iran

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Abstract

Introduction

Cancer patients often experience symptoms that adversely affect their quality of life. It is understood that many of these symptoms tend to cluster together: while they might have different manifestations and occur during different phases of the disease trajectory, the symptoms often have a common etiology that is a potential target for intervention. Understanding the symptom clusters (SCs) associated with cancer might usefully inform the development of effective care plans for affected patients.

Objective

Assess the SCs across a chemotherapy cycle in patients with gastrointestinal, breast, uterine, and ovarian cancers.

Methods

Longitudinal, descriptive study. 300 patients with gastrointestinal, breast, uterine, and ovarian cancers receiving chemotherapy were recruited with convenience sampling method. Data were collected in the week after chemotherapy. The symptom experience (occurrence and severity) was assessed using a modified version of the Memorial Symptom Assessment Scale (MSAS). SCs a hierarchical clustering approach visualized through a dendrogram

Results

A study of 300 patients (mean age 52.4 years, 51.3% female) with advanced cancers (32.3% gastrointestinal, 20.3% hematologic) identified five symptom clusters. The most intense and frequent symptoms were lack of energy, feeling drowsy, feeling sad, pain, and difficulty sleeping. Cluster 1 (largest) included digestive and respiratory issues. Cluster 2 related to appearance changes. Cluster 3 focused on gastrointestinal distress. Cluster 4 covered psychological and neurological symptoms. Cluster 5 comprised core distress symptoms, including pain and fatigue. Problems with sexual interest were not clustered.

Conclusion

Recognizing symptom clusters can inform comprehensive management strategies in advanced cancer care. Further studies are needed to validate and explore these clusters over time.

1. Introduction

Cancer is now one of the most important and dangerous chronic diseases in the world (1). According to the World Health Organization estimates in 2019, cancer was the second leading cause of death before the age of 70. Worldwide, approximately 19.3 million new cancer cases and almost 10 million cancer deaths occurred in 2020. The global cancer burden is projected to reach 28.4 million cases in 2040, a

47% increase compared to 2020 (2). The incidence of cancer is also increasing in Iran, with more than 30,000 patients currently dying from cancer annually (3, 4). Lung, prostate, colorectal, stomach, and liver cancers are the most common types of cancer in men, while breast, colorectal, lung, cervical, and thyroid cancers are the most common cancers in women (5).

These patients rarely present with a single symptom and usually experience multiple symptoms (poly-symptomatic) at the same time due to the disease or its treatments, such as chemotherapy and radiotherapy, which makes them difficult to manage (6). Symptoms in these patients usually occur in clusters that intensify or create a synergistic effect to produce new or more severe symptoms (7). These complications, in turn, cause further negative effects that not only affect the functional status and quality of life of the patient but also affect survival time (8). Symptom cluster was first proposed as a term to describe this phenomenon by Dodd et al. in 2001 (9). According to Kim et al., a “symptom cluster” refers to the simultaneous occurrence of two or more symptoms that may or may not have the same cause. Symptom clusters (SCs) are composed of stable groups of symptoms, are relatively independent of other clusters, and may reveal specific underlying concepts of symptoms. The relationships between symptoms within a cluster should be stronger than the relationships between symptoms across different clusters (10). The results of a systematic review by So et al. (2021) showed that sleep disturbance, fatigue, and psychological SCs (including anxiety, depression, nervousness, irritability, sadness, worry) were the most common SCs reported among breast cancer patients (11). The results of a study by Fu et al. (2022) conducted on 322 patients with gastric cancer undergoing chemotherapy identified five clusters based on symptom prevalence (12). In a study of symptom burden in 30 patients in Zhou et al. (2023), 42 symptoms were reported with an incidence of 86.7%, of which the five most common symptoms were: memory loss, enuresis, fatigue, distress, and dry mouth. Based on the incidence and severity of symptoms, 9 SCs were identified (13). Compared with a single symptom, a symptom cluster works together to increase patient suffering and financial distress, reduce treatment compliance, and even shorten survival. As a result, SCs have received increasing attention in recent years in an effort to reduce the negative consequences associated with symptoms (14). Symptom cluster research is an emerging field in symptom management that may advance the mechanisms and/or management of cancer-related symptoms, and attention to SCs may provide potential insights into symptom management (15–17).

By understanding SCs, oncology nurses can make more comprehensive assessments and prioritize care planning, reducing overall symptom burden. Awareness of SCs is helpful in developing nursing processes and in making decisions about palliative care. Awareness of clusters helps in identifying patients who require more specialized care, and also helps in making decisions to predict the appropriate care plan and to target and individualize interventions, which ultimately leads to improved quality of life for patients (18, 19). The study of SCs can advance cancer symptom management and open new avenues for managing multiple symptoms and may also aid in cancer diagnosis and prognosis. The occurrence of SCs may guide the selection of management strategies (20). A review of studies shows that studies have been conducted to identify SCs in some types of cancer. Therefore, the

researchers decided to conduct this study with the aim of determining and identifying clusters of symptoms in patients with gastrointestinal, breast, uterine, and ovarian cancers.

2. Materials and Methods

2 – 1.**Type of Research**

This research was of a descriptive-analytical study.

2–2. Place and Time of Research

In this study, the research setting included the oncology department of Kashani Teaching Hospital affiliated with Shahrekord University of Medical Sciences, private offices of hematologists and oncologists in Shahrekord, and the Specialized Cancer Center of Shafa Hospital affiliated with Jundishapur University of Medical Sciences in Ahvaz. This study was conducted between 1 May and 30 February 2025.

2–3. **Population and Sample**

To estimate the sample size in factor analysis studies that have many variables, one method is to use a rule of thumb that states that at least 3 to 20 subjects should be considered for each item to avoid computational problems (7, 21). The Memory Symptom Assessment Scale (MSAS) questionnaire generally assesses 32 symptoms, which, considering 3 to 20 subjects for each item, the required sample size is estimated to be between 96 and 640 people. The minimum sample size required to perform exploratory factor analysis is 300 patients. In this study, 300 patients were selected by convenience and based on the inclusion criteria. The inclusion criteria for the participants were as follows: 1) 18 years of age or older, 2) confirmed pathologic diagnosis of gastrointestinal, breast, uterine, and ovarian cancers, 3) receiving chemotherapy, 4) having already received chemotherapy, and 5) able to understand the study and give informed consent.

2–4. **Data Collection Tools**

The data collection tool in this study was a clinical and demographic profile form including (age, gender, and marital status, type of cancer, type of treatment, place of residence, education, and duration of cancer diagnosis) and the Memorial Symptom Assessment Scale (MSAS). The Memorial Symptom Assessment Scale (MSAS) is a self-report questionnaire desymptomed to measure the multidimensional experience of symptoms and was desymptomed by Portenoy et al. in 1994. This questionnaire includes 32 common symptoms in two parts. The first part includes 24 symptoms that include three aspects of occurrence (frequency), severity, and distress for each symptom. The second part includes 8 symptoms that are assessed only in terms of severity and distress, including mouth ulcers, changes in taste, weight loss, hair loss, constipation, swelling of the hands and feet, skin changes, and the phrase I don't feel like myself. Using the MSAS, patients are asked to indicate whether they have experienced each symptom in the past week or not (i.e., symptom occurrence). If they have experienced the symptom, they are asked

to rate its frequency, severity, and distress. Distress refers to whether the symptom has caused the patient any trouble or distress. The questionnaire is scored on a Likert scale. Each symptom is rated using a four-point rating scale for frequency and severity and a five-point scale for distress. Higher scores indicate greater frequency, greater severity, and higher levels of distress. The first 24 symptoms are scored as follows: in the frequency aspect, rarely = score 1, sometimes = score 2, often = score 3, and always = score 4; in the severity aspect, mild = score 1, moderate = score 2, severe = score 3, and very severe = score 4; and in the distress aspect, not at all = score 0, very little = score 1, little = score 2, much = score 3, and very much = score 4. The 8-symptom scoring of the second part is also measured in terms of severity and distress, which is the same as the first part. It also has an open-ended question at the end, asking patients to list any other symptoms they have besides these 32 (22). The MSAS is a valid and reliable measure of symptom experience in cancer populations, with Cronbach's alpha ranging from 0.83 to 0.88, making it suitable for clinical use (21). The reliability and validity of the MSAS have been well established in studies of oncology inpatients and outpatients (6, 23, 24). The validity and reliability of this questionnaire in cancer patients in Iran have also been tested by Bahrami et al. through face validity and exploratory factor analysis and reliability using internal correlation coefficients, with a Cronbach's alpha of 0.77 (25).

The method of completing the clinical and demographic characteristics form and the Recall Symptom Assessment Scale (MSAS) questionnaire was explained to the patient and the patients were asked to complete it as a self-report. For patients who were illiterate, this scale was read to the patient by the researcher and the patient was asked to choose the correct answer. Data were collected in the week before the patients' second or third cycle of chemotherapy.

2–5. Analysis of Data

Data analysis was conducted using SPSS. Descriptive statistics including mean, standard deviation, and frequency distributions were employed to summarize both quantitative and qualitative variables. Cluster analysis was applied to detect SCs, with a hierarchical clustering approach visualized through a dendrogram.

2–6. **Ethical consideration**

This study was approved by the Ethics Committee of Shahrekord University of Medical Sciences (ethical code: IR.SKUMS.REC.1404-004). The study objectives were explained to patients and the confidentiality was emphasized. Written consent were obtained from patients.

3. Results

Demographic and clinical characteristics of the participants are summarized in Table 1. The mean age of patients was 52.37 ± 14.59 years, and 51.3% of participants were female. The most common primary cancer sites were gastrointestinal (32.3%) and hematologic (20.3%). Lack of energy, feeling drowsy, feeling sad, pain, difficulty sleeping, and problems with sexual interest or activity had the highest mean

intensity scores. In terms of occurrence, the most frequently reported symptoms were lack of energy, feeling drowsy, difficulty sleeping, and feeling sad.

Table 1
Demographic and Clinical Characteristics of participants (n = 300)

Characteristics	Mean and SD / Frequency and percent
Age (years)	52.37 ± 14.59
Gender	
Male	146 (48.7%)
Female	154 (51.3%)
Primary cancer site	
Breast	46 (15.3%)
Lung	36 (12.0%)
Genitourinary	13 (4.3%)
Head and neck	10 (3.3%)
Gastrointestinal	97 (32.3%)
Gynecologic	19 (6.3%)
Hematologic	61 (20.3%)
Bone	18 (6.0%)
Undergoing Chemotherapy	
Yes	300 (100%)
No	0 (0%)
Time since diagnosis (months)	18.98 ± 23.52

Figure 2 presents the dendrogram of the identified SCs, indicating the presence of five clusters. Cluster 1 was the largest cluster, included symptoms of *diarrhea, difficulty swallowing*, *mouth sores, problems with urination, swelling of arms or legs, difficulty concentrating, dizziness, itching, changes in skin*, *sweats, cough*, and *shortness of breath.* Cluster 2 included symptoms of *hair loss*, and *"I don't look like myself"*. Cluster 3 included symptoms of *feeling bloated*, *constipation, lack of appetite*, *weight loss, nausea, vomiting, change in the way food tastes*, and *dry mouth.* Cluster 4 included symptoms of *feeling nervous*, *feeling irritable*, and *numbness/tingling in hands or feet.* Cluster 5 included symptoms of *pain, feeling drowsy, lack of energy, difficulty sleeping, feeling sad*, and *worrying. Problems with sexual interest or activity* remined single and was not placed in any cluster.

4. Discussion

In the present study, five SCs were identified based on their severity in adults with gastrointestinal, breast, uterine, and ovarian advanced cancers. The pattern obtained from symptom clustering in patients with advanced cancer in this study indicates that the symptom experience in these patients is multidimensional and interconnected, and cannot be solely attributed to isolated events. The formation of five distinct clusters suggests that symptoms act as interactive networks and likely stem from common biological and psychological mechanisms. The first cluster, encompassing the broadest set of symptoms, combines symptoms from different bodily systems and may indicate the activation of inflammatory pathways or the progression of disease burden. The second cluster included changes related to body image, reflecting the psychological impact of cancer and its treatments on patients' self-perception. The third cluster indicated the simultaneous occurrence of gastrointestinal and nutritional disorders in patients, which is one of the most common observed clusters in cancer patients (26). The fourth cluster, including symptoms of anxiety, irritability, and sensory disturbances, likely reflects the complex interplay between neurological factors and psychological stress. The fifth cluster includes fatigue, sleep disturbance, pain, and depressed mood, which is repeatedly recognized as one of the most persistent SCs in cancer and has a significant impact on daily functioning (27–29). Meanwhile, the non-association of sexual activity problems with any of the clusters suggests that this symptom may have a different co-occurrence pattern due to cultural, psychological, or interpersonal reasons.

In line with our study's findings, several studies have identified nearly similar cluster compositions in different patient subgroups (30–32). These findings indicated that the occurrence of these clusters, irrespective of cancer type, may share a common mechanism or a common cause.

The findings showed that the most prominent symptoms in terms of severity and occurrence mainly fall within three main domains: fatigue–sleep disturbance, pain, and mood-related discomfort. The high recurrence of low energy, drowsiness, and difficulty sleeping, alongside the high intensity of these symptoms, suggests that patients are likely involved in a persistent cycle of both physiological and psychological disturbances that mutually reinforce each other. At the same time, the high severity of pain further complicates this cycle, because evidence indicates that uncontrolled pain can both reduce sleep quality and exacerbate fatigue and low mood (33, 34). This pattern highlights the importance of integrated approaches in palliative care and symptom management an approach that addresses fatigue, sleep, mood, and pain simultaneously, in order to stop or at least weaken the ongoing cycle of ill-being. The presence of problems related to sexual interest or activity among the symptoms with the highest mean severity is also a noteworthy finding. Although this area is often less reported or less studied, it underscores the need for greater clinical attention to patients' sexual needs, which are typically neglected in routine care.

The use of more comprehensive tools like MSAS in the present study is a significant advantage compared to brief instruments. Employing concise instruments can lead to the identification of oversimplified clusters, as a limited range of symptoms may not provide full coverage of the broad

spectrum of symptoms experienced by patients with advanced cancer. The omission or non-measurement of certain key symptoms could result in an incomplete identification of clusters or the artificial merging of heterogeneous symptoms into a single cluster. In contrast, MSAS, by offering a wider and more representative set of symptoms, enables the identification of more realistic and complex patterns of symptom co-occurrence, thereby enhancing the accuracy and validity of cluster analysis. Therefore, the findings of this study can be interpreted in light of the utilization of a more comprehensive assessment tool. This tool, by covering numerous and diverse symptoms, reduces the potential bias arising from the limitations of symptom range and allows for the extraction of clusters that offer a more accurate reflection of the symptom experience in patients with advanced cancer, especially given that patients with advanced cancer often experience multiple symptoms simultaneously. Chen et al.'s study used the Edmonton Symptom Assessment System (ESAS), which assesses only nine symptoms, to identify symptom clusters in patients with advanced cancer. This limitation in clustering may arise due to the wide range of symptoms these patients experience (35).

In future research, focusing on identifying the causal relationships between symptoms within each cluster will be a vital step toward enhancing clinical decision-making for effective symptom management in patients with advanced cancer. This approach allows for the distinction between central (core) symptoms that have widespread effects on other symptoms within the cluster and the entire cluster, and peripheral symptoms that have less impact on the cluster's dynamics. For instance, targeting one symptom might influence other symptoms and the entire cluster, while another symptom within the cluster might be peripheral, with targeting it having no effect on other symptoms within the cluster. Understanding these relationships enables clinicians to strategically focus their therapeutic interventions on key symptoms, thereby maximizing treatment efficacy. Consequently, determining the core and peripheral symptoms in each cluster can serve as a valuable guide for designing targeted and personalized treatment protocols.

Overall, the pattern obtained from symptom co-occurrence indicates that patients with advanced cancer face a complex and multi-layered network of symptoms that reinforce each other, exacerbating the disease burden. Interpreting the clusters and considering the role of core symptoms can provide a new path for understanding the underlying mechanisms of these co-occurrences and offer a practical framework for designing targeted interventions. Emphasizing integrated management, exploring cause-and-effect relationships, and focusing on key symptoms within each cluster can contribute to improving quality of life, enhancing treatment outcomes, and advancing palliative care. These results suggest that future approaches should move towards cluster-based and individualized treatments to effectively reduce the symptom burden in these patients.

4 − 1. **Study limitations**

Among the limitations of this study is that its cross-sectional desymptom does not allow for the inference of causal relationships between symptoms or the dynamics of their changes. The data were collected based on patient self-reports and are therefore subject to biases related to individual perception, fatigue, or psychological state. The inclusion criteria considered may have led to the

exclusion of severely ill patients. The exclusion of this group could result in an underestimation of the true symptom burden, as individuals with severe disabilities usually face higher intensity and more complex symptom patterns. Therefore, the study's results may not reflect a complete and accurate picture of the true symptom burden across the full spectrum of patients with advanced cancer.

5. Conclusion

This study, by identifying distinct clusters of co-occurring symptoms in patients with four types of advanced cancer, provides a practical framework for better understanding the complex experience of these patients. Our findings suggest that symptoms often manifest as an interconnected set, and focusing solely on each symptom in isolation may not be sufficient. Understanding these symptom clusters can help treatment teams adopt multifaceted assessment and intervention approaches for patients with advanced cancer. Despite the limitations of the cross-sectional desymptom and sample characteristics, the study's results offer valuable insights into the symptom structure in patients with advanced cancer and can serve as a basis for developing more personalized treatment protocols to improve the quality of life for patients with advanced cancer. Future research should focus on confirming these clusters in larger and more diverse populations, investigating the effectiveness of targeted interventions for each cluster, and elucidating the dynamic relationships between symptoms over time. Furthermore, future studies should concentrate on identifying and targeting core symptoms within the clusters.

Declarations

Disclosure

All authors have agreed on the final version.

Ethics Statement

Written ethical and institutional permissions were obtained from the Shahrekord University of Medical Sciences Ethics Committee (ethical code: IR.SKUMS.REC.1404-004). The study objectives were explained to patients, and confidentiality was emphasized. Written informed consent was obtained from patients. The Helsinki Declaration ethical principles were adhered throughout the research process.

Conflicts of Interest

The authors declare no conflicts of interest.

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Author Contribution

All authors meet at least one of the following criteria (recommended by the ICMJE [http://www.icmje.org/recommendations/]): substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data and drafting the article or revising it critically for important intellectual content.

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Data Availability

The data that support the findings of this study are available from the Corresponding author upon reasonable request

References

1. Sathishkumar, K., Chaturvedi, M., Das, P., Stephen, S. & Mathur, P. Cancer incidence estimates for 2022 & projection for 2025: Result from National Cancer Registry Programme, India. *Indian J. Med. Res.* **156** (4&5), 598–607 (2022).
2. World Health Organization. Global health estimates: Leading causes of death. by Country and by Region. https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/ghe-leading-causes-of-death [.
3. Farhood, B., Geraily, G. & Alizadeh, A. Incidence and Mortality of Various Cancers in Iran and Compare to Other Countries: A Review Article. *Iran. J. public. health*. **47** (3), 309–316 (2018).
4. Khanali, J. & Kolahi, A. A. National and Subnational Cancer Incidence for 22 Cancer Groups, 2000 to 2016: A Study Based on Cancer Registration Data of Iran. *J. cancer Epidemiol.* **2021**, 6676666 (2021).
5. https://www.who.int/health-topics/cancer#tab=tab_1
6. Snijders, R. A. H., Brom, L., Theunissen, M. & van den Beuken-van Everdingen, M. H. J. Update on Prevalence of Pain in Patients with Cancer 2022: A Systematic Literature Review and Meta-Analysis. *Cancers* ;**15**(3). (2023).
7. Özalp, G. et al. Identification of Symptom Clusters in Cancer Patients at Palliative Care Clinic. *Asia-Pacific J. Oncol. Nurs.* **4** (3), 259–264 (2017).

8. Harris, C. S. et al. Symptom clusters in oncology outpatients: stability and consistency across a cycle of chemotherapy. *BMJ supportive Palliat. care*. **13** (e3), e1198–e211 (2024).
9. Dodd, M. et al. Advancing the science of symptom management. *J. Adv. Nurs.* **33** (5), 668–676 (2001).
10. Kim, H. J., McGuire, D. B., Tulman, L. & Barsevick, A. M. Symptom clusters: concept analysis and clinical implications for cancer nursing. *Cancer Nurs.* **28** (4), 270–282 (2005). quiz 83–4.
11. So, W. K. W. et al. Symptom clusters experienced by breast cancer patients at various treatment stages: A systematic review. *Cancer Med.* **10** (8), 2531–2565 (2021).
12. Fu, L. et al. Symptom Clusters and Quality of Life in Gastric Cancer Patients Receiving Chemotherapy. *J. Pain Symptom Manag.* **63** (2), 230–243 (2022).
13. Zhou, K. N. et al. Symptom burden survey and symptom clusters in patients with cervical cancer: a cross-sectional survey. *Supportive care cancer: official J. Multinational Association Supportive Care Cancer*. **31** (6), 338 (2023).
14. Guo, M., Wang, C., Yin, X., Nie, L. & Wang, G. Symptom clusters and related factors in oesophageal cancer patients 3 months after surgery. *J. Clin. Nurs.* **28** (19–20), 3441–3450 (2019).
15. Hooke, M. C. et al. Symptom Clusters, Physical Activity, and Quality of Life: A Latent Class Analysis of Children During Maintenance Therapy for Leukemia. *Cancer Nurs.* **45** (2), 113–119 (2022).
16. Miladinia, M. et al. A multiphase study protocol of identifying, and predicting cancer-related symptom clusters: applying a mixed-method design and machine learning algorithms. *Front. Digit. Health* ;Volume 6–2024. (2024).
17. Sattari, A., Miladinia, M., alinejad mofrad, S., Akbari, S. & Ahmadi-Mazhin, S. Nursing Perspectives on Cancer-related Symptom Management in Palliative Care: A State-of-the-Art (SotA) Review Focused on Iran. *Jundishapur J. Chronic Disease Care* ;**14**. (2025).
18. Ghafoor, I., Hafeez, H., Naz, F., Abubakar, M. & Jamshed, A. Prevalence of Symptom Clusters in Cancer Patients at First Presentation in Palliative Care Clinic as per Different Disease Groups. *J. Cancer Immunol.* **1** (1), 1–11 (2019).
19. Kim, H. J., Barsevick, A. M., Beck, S. L. & Dudley, W. Clinical subgroups of a psychoneurologic symptom cluster in women receiving treatment for breast cancer: a secondary analysis. *Oncol. Nurs. Forum*. **39** (1), E20–30 (2012).
20. Tabudlo, J. B. A Proposed Theory of Symptom Cluster Management. *Belitung Nurs. J.* **7** (2), 78–87 (2021).
21. Chaiviboontham, S., Phinitkhajorndech, N. & Tiansaard, J. Symptom Clusters in Patients with End-Stage Renal Disease Undergoing Hemodialysis. *Int. J. Nephrol. renovascular disease*. **13**, 297–305 (2020).
22. Pett, M. A., Lackey, N. R. & Sullivan, J. J. Designing and testing the instrument. In M. A. PettN. R. Lackey, & J. J. Sullivan Designing and testing the instrument. SAGE Publications, Inc, https://dxdoiorg/104135/9781412984898. (2003).

23. Englehart, V., Noonan, D., Schneider, S. M. & Thompson, J. Implementing the Condensed Memorial Symptom Assessment Scale on an Inpatient Oncology Unit. *Clin. J. Oncol. Nurs.* **26** (1), E1–e6 (2022).
24. Hayase, T. et al. Reliability and Validity of the Japanese Pediatric Version of Memorial Symptom Assessment Scale. *J. Pain Symptom Manag.* **63** (5), e495–e504 (2022).
25. Bahrami, M., Assarroudi, M. & Mahmoodzadeh, M. Investigation of Symptoms' Frequency, Severity, and Distress in Patients with Leukemia Admitted to Hematology-Oncology Wards of Selected Hospitals in Isfahan, Iran, in 2016. *J. Health Syst. Res.* **13** (2), 140–145 (2017).
26. Li, R., Ma, J., Chan, Y., Yang, Q. & Zhang, C. Symptom Clusters and Influencing Factors in Children With Acute Leukemia During Chemotherapy. *Cancer Nurs.* **43** (5), 411–418 (2020).
27. Shushtari, S. S. G. et al. Comparing Massage, Acupressure, and Combined Therapy for Managing Cancer-related Pain, Fatigue, and Sleep Disturbance: A 2 × 2 Factorial Randomized Controlled Trial. *Int. J. Ther. Massage Bodyw.* **18** (4), 31–44 (2025).
28. Lai, Q. et al. Experiences of the fatigue-pain-sleep disturbance symptom cluster among patients with lung cancer: A descriptive qualitative study. *Asia-Pacific J. Oncol. Nurs.* **12**, 100823 (2025).
29. Ye, Y. et al. Differential Characteristics of Fatigue-Pain-Sleep Disturbance-Depression Symptom Cluster and Influencing Factors of Patients With Advanced Cancer During Treatment: A Latent Class Analysis. *Cancer Nurs.* **48** (5), 352–359 (2025).
30. Nongluck, S. et al. Symptom Clusters and Functional Status of Women with Breast Cancer Thai. *J. Nurs. Res.* **12** (3), 153–165 (2008).
31. Ward Sullivan, C. et al. Differences in symptom clusters identified using symptom occurrence rates versus severity ratings in patients with breast cancer undergoing chemotherapy. *Eur. J. Oncol. nursing: official J. Eur. Oncol. Nurs. Soc.* **28**, 122–132 (2017).
32. Wong, M. L. et al. Differences in Symptom Clusters Identified Using Ratings of Symptom Occurrence vs. Severity in Lung Cancer Patients Receiving Chemotherapy. *J. Pain Symptom Manag.* **54** (2), 194–203 (2017).
33. Seiger, A. N., Penzel, T. & Fietze, I. Chronic pain management and sleep disorders. *Cell. Rep. Med.* **5** (10), 101761 (2024).
34. Miladinia, M., Baraz, S., Ramezani, M. & Malehi, A. S. The relationship between pain, fatigue, sleep disorders and quality of life in adult patients with acute leukaemia: During the first year after diagnosis. *Eur. J. Cancer Care*. **27** (1), e12762 (2018).
35. Chen, E. et al. Symptom clusters in patients with advanced cancer: sub-analysis of patients reporting exclusively non-zero ESAS scores. *Palliat. Med.* **26** (6), 826–833 (2012).

Figures

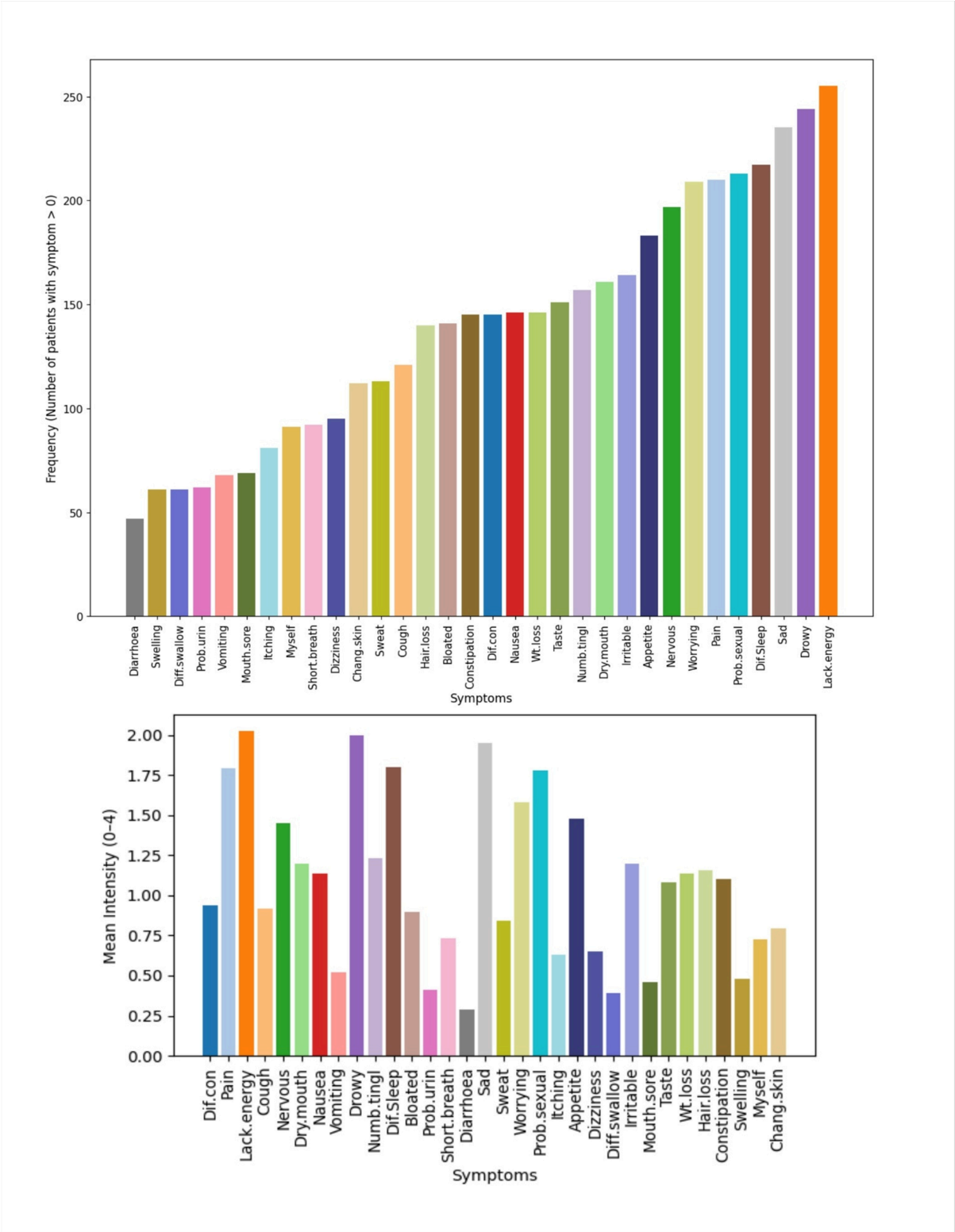


Figure 1

Occurrence and mean intensity (0 to 4) of each symptom

Abbreviations: Dif (difficulty); Constipat (constipation); Wt (weight); Myself (I don't look like myself); Numb.tingl (Numbness/tingling in hands/feet); Prob (problem)

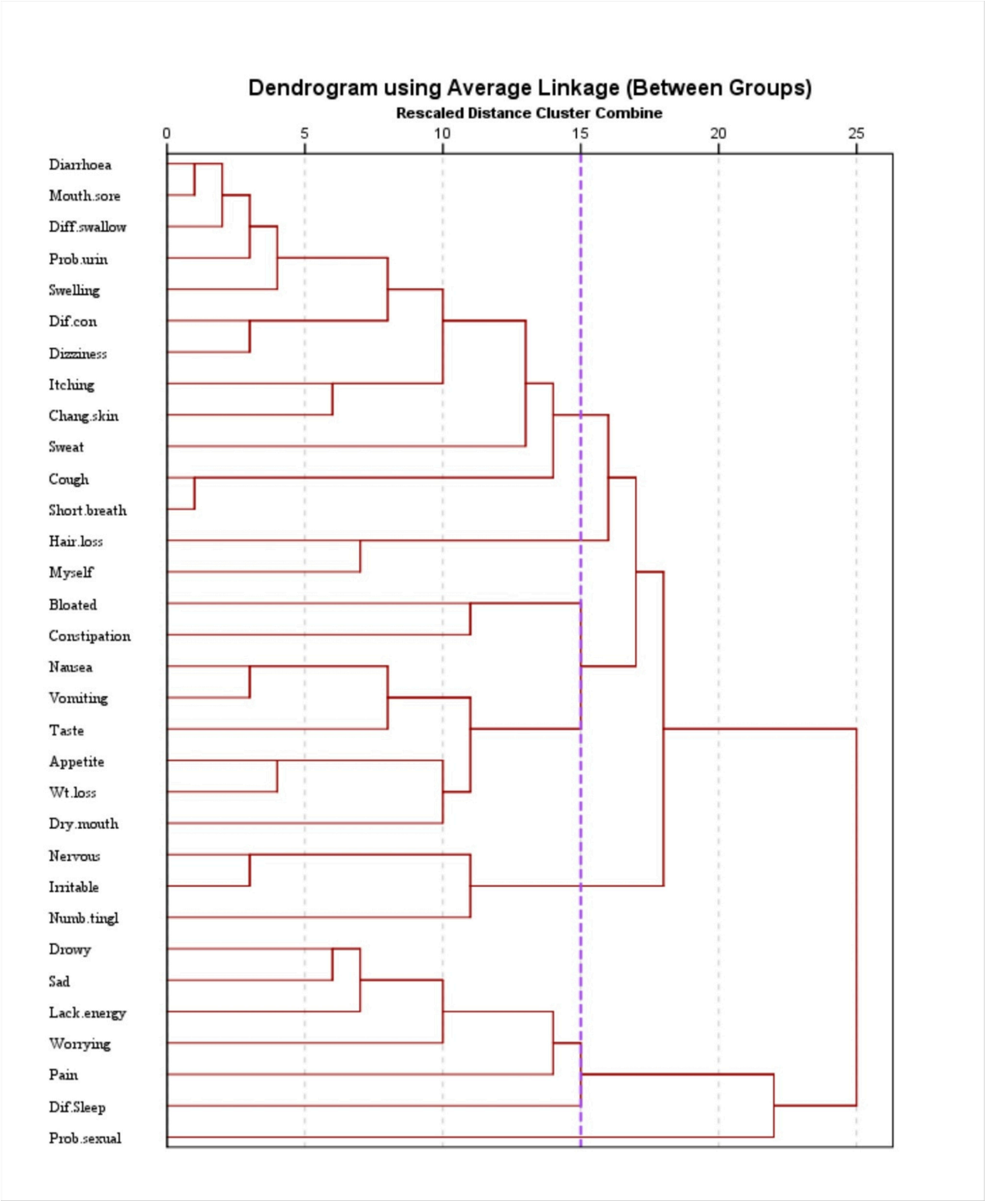


Figure 2

Dendrogram for clustering on the basis of cut-off level

Abbreviations: Dif (difficulty); Wt (weight); Myself (I don't look like myself); Numb.tingl (Numbness/tingling in hands/feet); Prob (problem)