



Symptom Clustering and Its Association with Treatment and Comorbidities in Advanced Head and Neck Cancer Patients: A Data-Driven Analysis

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Abstract

Introduction Head and neck cancers (HNCs) are frequently associated with a complex symptom burden caused by both the disease and its treatment modalities, including surgery, radiotherapy, and chemotherapy. These symptoms often appear in clusters rather than as isolated events, considerably impairing patients' quality of life. Identifying these symptom clusters and understanding their relationships with treatment types and comorbidities is crucial for improving targeted symptom management.

Objective The aim of this study was to identify symptom clusters in patients with advanced HNC and evaluate their associations with treatment modalities and coexisting health conditions.

Materials and Methods A prospective observational study was conducted at the Department of Palliative Care, Kolhapur Cancer Center, from August 2021 to August 2024. A total of 400 patients with HNC undergoing chemotherapy, radiotherapy, or both were included. Symptom data were collected using the Edmonston Symptom Scale, evaluating pain, fatigue, nausea, depression, anxiety, anorexia, weight loss, dysphagia, and voice changes. Patient demographics, treatment details, and comorbidities (diabetes, hypertension, and ischemic heart disease) were recorded. Statistical analyses included exploratory factor analysis, K-means, and hierarchical clustering to identify symptom patterns. Associations were analyzed using ANOVA and chi-square tests.

Results Five distinct symptom clusters were identified: (1) high symptom burden, (2) pain and swallowing difficulties, (3) nausea and anxiety dominant, (4) fatigue with swallowing issues, and (5) weight loss with severe dysphagia. Radiotherapy was significantly associated with clusters involving dysphagia and weight loss ($p < 0.0001$). Diabetes ($p = 0.0010$) and hypertension ($p < 0.0001$) were also significantly related to increased symptom severity. Chemotherapy showed no significant association with symptom

Keywords

- ▶ head and neck cancer
- ▶ symptom clusters
- ▶ radiotherapy
- ▶ chemotherapy
- ▶ palliative care
- ▶ comorbidities
- ▶ symptom management

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clustering. Hierarchical clustering and principal component analysis confirmed the consistency of these patterns.

Conclusion The study emphasizes the clinical value of recognizing symptom clusters in patients with HNC. Significant associations with radiotherapy and comorbid conditions suggest the need for tailored symptom management strategies. Future research should focus on longitudinal tracking and the integration of machine learning techniques to further refine symptom classification and personalize care.

Introduction

Head and neck cancer (HNC) encompasses a range of malignancies that arise in anatomical regions such as the oral cavity, pharynx, larynx, and related structures. It is frequently accompanied by a substantial symptom load, stemming not only from the cancer itself but also from its treatments, including surgery, radiotherapy, and chemotherapy. These symptoms often present in clusters rather than independently, leading to a notable decline in patients' overall quality of life.^{1–3}

Symptom clusters are defined as groups of interrelated symptoms that may result from shared pathophysiological mechanisms or similar treatment effects. For instance, radiotherapy commonly leads to complications such as dysphagia, voice alterations, and unintended weight loss. Conversely, patients undergoing chemotherapy are more likely to experience fatigue, nausea, and reduced appetite.^{4–6} Emotional distress is also prevalent, with pain, anxiety, and depression frequently co-occurring and amplifying the overall symptom burden.

Identifying and understanding these symptom clusters is critical for enhancing the effectiveness of symptom management and ensuring comprehensive supportive care. In addition to treatment modalities, factors such as age and comorbid health conditions substantially affect the pattern and intensity of symptoms. Older adults may face exacerbated symptoms due to physiological decline, while younger individuals may exhibit different tolerance levels to treatment. Chronic illnesses such as diabetes, hypertension, and ischemic heart disease also modulate symptom expression—diabetes is often linked with increased fatigue and delayed tissue recovery, whereas hypertension can heighten cardiovascular strain.^{1,3–7}

Among therapeutic interventions, radiotherapy has been particularly associated with persistent and distressing symptoms such as mucositis, xerostomia, and swallowing difficulties.⁵ Gaining deeper insights into the interaction between symptoms, treatment types, and patient-specific factors is essential for the development of personalized symptom control strategies aimed at improving health-related quality of life in patients with HNC.

Materials and Methods

Study Design and Setting

This research employed a prospective observational design and was conducted at the Department of Palliative Care, Kolhapur Cancer Center—a dedicated oncology institution

offering both cancer therapies and supportive care. Data collection spanned 3 years, from August 2021 to August 2024, capturing real-time symptom profiles of patients undergoing treatment for HNC.

Study Population and Sample Size

The study included 400 patients diagnosed with HNC, who were followed up longitudinally during their treatment and subsequent visits to the palliative care unit.

Inclusion Criteria

Confirmed diagnosis of HNC (any stage).

Age 18 years or older.

Receiving chemotherapy, radiotherapy, or both.

Willingness to participate and provide informed consent.

Regular attendance at the palliative care clinic for symptom monitoring.

Exclusion Criteria

Preexisting neurological or psychiatric disorders that could interfere with symptom reporting.

Patients lost to follow-up or those who discontinued therapy.

Individuals with recurrent or metastatic disease undergoing experimental treatment regimens.

Data Collection and Symptom Assessment

Symptom-related data were gathered using the Edmonston Symptom Scale, a validated tool widely adopted in palliative care for systematic symptom monitoring. The symptoms evaluated included pain, fatigue, nausea and vomiting, anxiety, depression, anorexia, weight loss, dysphagia (difficulty swallowing), voice changes, neck swelling, and sore throat. Each symptom was marked as present or absent and categorized by severity.

Severity grading was based on a numeric scale from 0 to 10: scores of 0 to 3 denoted mild symptoms, 4 to 6 represented moderate, and values ≥ 6 indicated severe symptoms. Alongside symptom data, patient demographics (e.g., age, gender), treatment specifics (e.g., chemotherapy and radiotherapy), and the presence of comorbid conditions (e.g., diabetes, hypertension, ischemic heart disease) were also recorded to evaluate their influence on symptom clustering.

The Edmonston Symptom Scale demonstrated strong psychometric properties, with a Cronbach's alpha of 0.87 (indicating high internal consistency) and an inter-rater reliability score of 0.85, confirming consistency among

different evaluators. Its numeric rating system facilitates accurate tracking of symptom severity and changes over time, enabling timely clinical interventions. The scale's reliability and applicability make it particularly useful for identifying clusters of co-occurring symptoms in patients with HNC.

Statistical Analysis

Multiple statistical approaches were applied to identify and validate symptom cluster patterns. Exploratory factor analysis was first conducted to uncover latent groupings among symptoms. Patients were then grouped into distinct clusters using K-means clustering, with validation through hierarchical clustering based on Ward's Method. Latent Class Analysis (LCA) was also applied to investigate alternative symptom cluster configurations.

To assess associations between symptom clusters and demographic or clinical variables, the ANOVA/Kruskal–Wallis test was used for continuous variables such as age, while the chi-square test evaluated relationships between symptom clusters and treatment modalities (chemotherapy, radiotherapy) or comorbidities (diabetes, hypertension, ischemic heart disease). The optimal number of clusters was determined using Silhouette Score Analysis, and symptom relationships were visually explored using dendrograms generated from hierarchical clustering outputs.

Ethical Considerations

This study was approved by the Institutional Ethics Committee of Kolhapur Cancer Center under approval number ECR/523/Inst/MH/2014/RR-20. Informed written consent was obtained from all participants. Patient confidentiality was strictly maintained through anonymization of data before analysis, ensuring that individual identities were not disclosed.

Results

► **Table 1** summarizes the most common symptoms and comorbidities among head and neck cancer patients. Fatigue (62.5%), anorexia (63.7%), and pain (58.5%) emerged as the most frequently reported symptoms, highlighting a substantial physical burden. Localized effects of the disease were reflected by difficulty swallowing (50.0%) and voice changes (55.2%). Mental health issues were also prominent, with anxiety (49.7%) and depression (33.7%) showing considerable prevalence, underlining the psychological toll of cancer. Among comorbidities, diabetes (32.7%) and hypertension (26.5%) were common, while ischemic heart disease (6.3%) was less frequent. These findings emphasize the need for integrated care addressing physical, psychological, and metabolic health issues.

The scree plot of principal component analysis (► **Fig. 1**) showed a gradual decline in explained variance without a clear “elbow point.” The first five components together accounted for 58% of the variance, indicating sufficient structure for clustering. K-means clustering was applied, and a five-cluster solution was selected based on a higher

Table 1 Prevalence of common symptoms and comorbidities among patients with head and neck cancer

Category	Condition	Prevalence (%)
Symptom prevalence	Fatigue	62.5
	Anorexia	63.7
	Pain	58.5
	Difficulty swallowing	50.0
	Voice changes	55.2
	Anxiety	49.7
	Depression	33.7
Comorbidities	Diabetes mellitus	32.7
	Hypertension	26.5
	Ischemic heart disease	6.3

silhouette score (0.123) compared to the four-cluster solution (0.110). This ensured a more distinct separation of patient groups, forming the basis for further symptom characterization.

► **Table 2** details the five clusters identified. Cluster 0 represented patients with severe multi-symptom burden, with near-universal prevalence of pain (100%), fatigue (93%), depression (96%), and anorexia (94%). Cluster 1 reflected patients with moderate pain (80%) and swallowing difficulties, but with fewer systemic symptoms. Cluster 2 was characterized by nausea (75%) and anxiety (85%), while depression was rare. Cluster 3 primarily included patients with fatigue (71%) and swallowing difficulty (57%) but minimal emotional distress. Cluster 4 showed a distinct profile of severe weight loss (96%), often accompanied by fatigue and swallowing issues. Together, these patterns highlight the heterogeneity of symptom experiences in this patient population.

► **Fig. 2** illustrates hierarchical clustering, confirming the robustness of the five-cluster solution. Shorter branch lengths indicated close similarity within patient groups, whereas longer branches denoted distinct separation. The dendrogram showed well-differentiated subgroups of

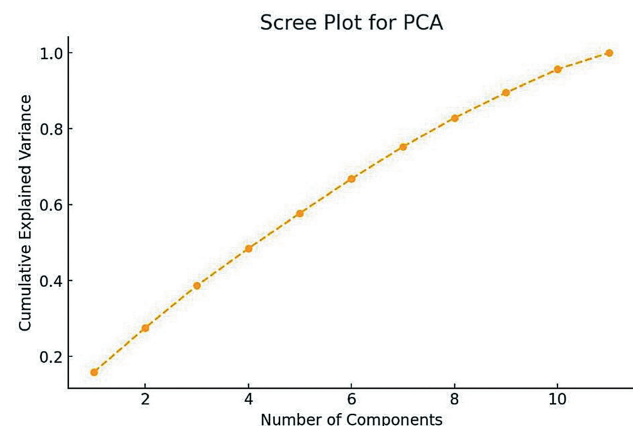


Fig. 1 Scree Plot for cluster identification for PCA.

Table 2 Symptom clusters in patients with head and neck cancer

Cluster	Key symptoms	Description
Cluster 0: severe multi-symptom burden	Pain (100%) Fatigue (93%) Depression (96%) Anorexia (94%) Significant nausea, anxiety, and sore throat (86%)	Patients experiencing widespread and severe symptom burden
Cluster 1: moderate pain and swallowing difficulties	Pain (80%) Difficulty swallowing (41%) Low nausea (0%) and anxiety (10%) Moderate weight loss (60%)	Patients with localized discomfort, mainly pain and swallowing issues, but fewer systemic symptoms
Cluster 2: nausea and anxiety dominant	Nausea (75%) Anxiety (85%) Moderate anorexia (65%) Low depression (0%)	Patients experiencing nausea-driven distress with significant anxiety
Cluster 3: fatigue and difficulty swallowing	Fatigue (71%) Difficulty swallowing (57%) Low pain (15%) Depression (27%)	Patients with swallowing-related discomfort and fatigue but less emotional distress
Cluster 4: severe weight loss and swallowing issues	Weight loss (96%) Fatigue (81%) Difficulty swallowing (59%)	Patients with significant weight loss and swallowing difficulties

patients, validating the K-means findings and reinforcing the presence of clinically meaningful symptom clusters.

The heatmap in ►Fig. 3 provides a visual comparison of symptom prevalence across clusters. Cluster 0 was marked by the highest overall symptom burden, particularly pain, fatigue, and depression. Cluster 4 was distinguished by extreme weight loss, suggesting nutritional challenges. Cluster 2 displayed high nausea and anxiety, defining a subgroup with a pronounced emotional and gastrointestinal symptom profile. This visualization underscores the

variability and intensity of symptom experiences across patient subgroups.

Cluster Comparisons and Statistical Associations

Comparative analysis across clusters revealed significant associations with patient and treatment characteristics. Age differences between clusters were statistically significant ($p < 0.001$), indicating that cluster membership is influenced by age. Radiotherapy was strongly associated with specific clusters ($p < 0.001$), confirming its role in shaping

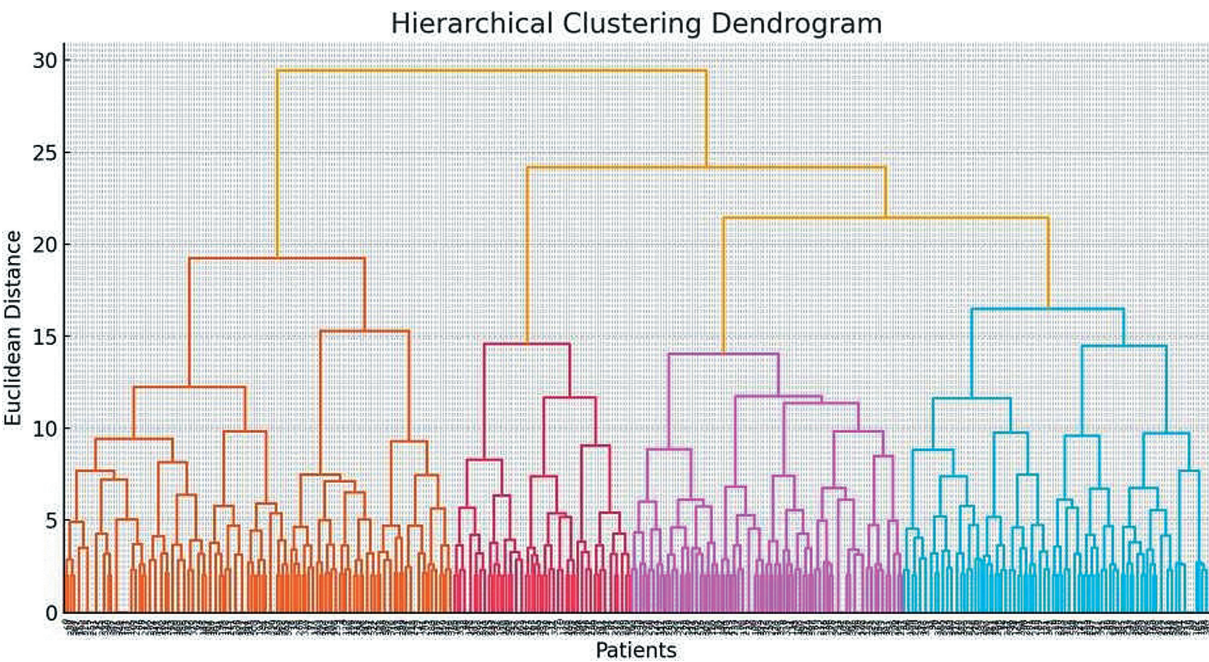


Fig. 2 Dendrogram indicating the clusters and their relation with each other.

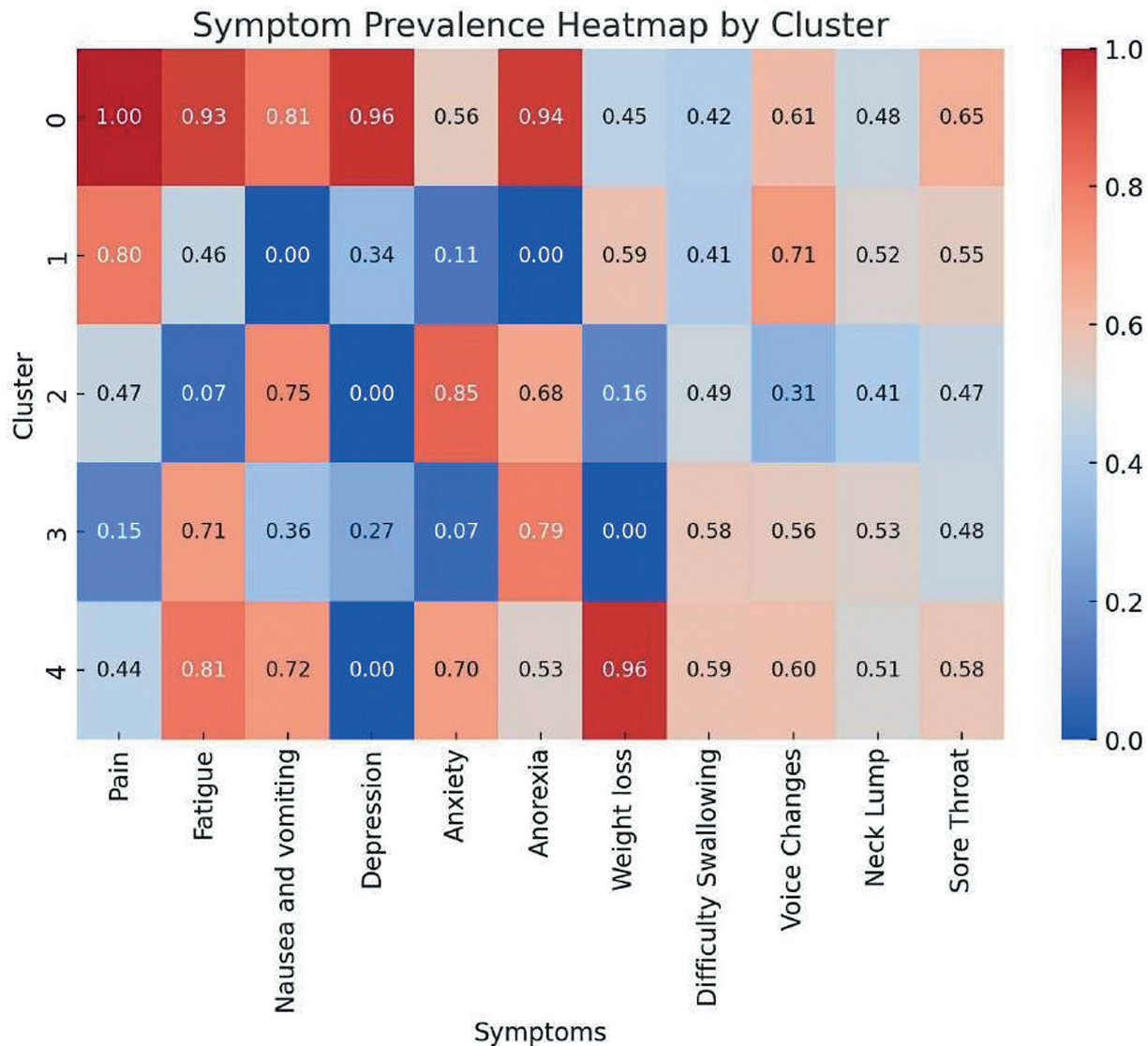


Fig. 3 Heat map showing symptom prevalence by cluster.

symptom patterns. Among comorbidities, diabetes ($p = 0.0010$) and hypertension ($p < 0.001$) were significantly linked to cluster distribution. In contrast, chemotherapy ($p = 0.679$) and ischemic heart disease ($p = 0.085$) did not show significant associations. These results demonstrate that patient age, radiotherapy exposure, and certain comorbidities contribute substantially to symptom clustering, providing important directions for personalized management.

Discussion

Symptom clustering in patients with HNC has been an area of increasing research interest, with various studies examining different methodologies and symptom groupings. Our study, conducted at the Department of Palliative Care, Kolhapur Cancer Center, aligns with and extends previous findings on symptom clusters, their stability, and their associations with treatment modalities and comorbidities. Several systematic reviews and observational studies have identified common

symptom clusters in HNC, focusing on general distress (fatigue, depression, and pain), treatment-related symptoms (mucositis, xerostomia, and difficult swallowing), and gastrointestinal issues (nausea, vomiting, and anorexia). Mathew et al⁸ identified three dominant symptom clusters—general, HNC-specific, and gastrointestinal.

Our study corroborated these findings by identifying similar clusters, particularly those emphasizing severe multi-symptom burden and nausea/anxiety-dominant symptoms. This reinforces the notion that specific symptom combinations frequently occur in this patient population.

Additionally, a study by Dong et al⁹ highlighted that symptoms within a cluster often co-occur in a non-random pattern, although they may not always share the same underlying cause. This observation aligns with our study, where clusters such as “fatigue and difficulty swallowing” and “nausea and anxiety” were identified. These findings suggest that while symptoms within a cluster may not have identical origins, they may share pathways of exacerbation, requiring integrated symptom management approaches.

Several studies, including those by Wang et al¹⁰ and Bressan et al,¹¹ have explored the relationship between symptom clusters and treatment modalities, particularly chemotherapy and radiotherapy.

Wang et al¹⁰ reported that symptoms specific to radiation therapy, such as oral mucositis and swallowing difficulty, were clustered together and significantly associated with weight loss. Our findings were consistent with this, demonstrating that patients experiencing severe weight loss also reported swallowing difficulties, reinforcing the impact of radiation therapy on symptom clustering.

Moreover, previous research has indicated that comorbid conditions such as diabetes and hypertension contribute to higher symptom burdens, likely due to underlying systemic inflammation.^{9,11,12} Our study similarly found a significant association between diabetes, hypertension, and specific symptom clusters, particularly those characterized by fatigue and pain. These results further support existing evidence that preexisting medical conditions can influence symptom severity and cluster formation in cancer patients. To validate the symptom clusters, our study employed hierarchical clustering and principal component analysis, methods that have been widely used in similar research. Studies by Xiao et al¹² and Chiang et al¹³ demonstrated that symptom clusters evolve over time, particularly during and after radiotherapy. Our study also observed fluctuations in symptom burden, with clusters changing in severity as treatment progressed. These findings emphasize the need for ongoing symptom monitoring to adjust management strategies in real time.

The consistent identification of symptom clusters across multiple studies, including our own, suggests that treatment approaches should focus on cluster-specific interventions rather than addressing individual symptoms in isolation.^{7,9,10,13} For instance, the commonly observed pain, fatigue, and depression cluster may benefit from integrated palliative care strategies, incorporating pharmacological, psychological, and supportive care interventions instead of treating each symptom separately.

Future research should emphasize longitudinal studies to track symptom evolution over extended periods, allowing for a better understanding of how symptom clusters change and how interventions should be adapted accordingly. Additionally, the integration of machine learning techniques, such as latent class analysis or self-organizing maps, could enhance the identification of symptom clusters and improve predictive modeling. These advanced methods could lead to more personalized symptom management strategies, ultimately improving the quality of life for patients with HNC.

Cluster-Specific Management Recommendations

Cluster 0: Severe Multi-Symptom Burden

Patients in this group experience intense physical and psychological symptoms, including pain, fatigue, anorexia, depression, nausea, anxiety, and sore throat. Comprehensive palliative care referral is critical. Multimodal pain management (e.g., opioids with adjuvants), antiemetics, and psycho-

tropic medications (antidepressants or anxiolytics) are essential. Nutritional support, including enteral feeding, should be initiated when anorexia and weight loss are severe. Psychological counseling, such as cognitive-behavioral therapy, is advised to address emotional distress.

Cluster 1: Moderate Pain and Swallowing Difficulties

These patients primarily report localized symptoms, especially pain and dysphagia. Treatment should focus on adequate analgesia and early dysphagia management.

Referral to a speech-language pathologist for swallowing exercises and dietary adjustments (soft or liquid diets) is recommended to maintain nutrition and prevent deterioration.

Cluster 2: Nausea and Anxiety Dominant

This group presents with prominent gastrointestinal and emotional symptoms. Symptom control should include personalized antiemetic regimens and anxiety management through medications (e.g., selective serotonin reuptake inhibitors or anxiolytics). Psychological support, including counseling and stress reduction techniques (e.g., mindfulness), may improve adherence and emotional resilience.

Cluster 3: Fatigue and Difficulty Swallowing

Patients here primarily struggle with energy loss and swallowing issues, with minimal emotional symptoms. Management should include energy conservation strategies via occupational therapy and nutritional enhancement with high-protein, high-calorie supplements. Swallowing rehabilitation and assessment for reversible causes of fatigue (e.g., anemia, thyroid dysfunction) should be part of routine care.

Cluster 4: Severe Weight Loss and Swallowing Issues

This cluster reflects a subgroup at high nutritional risk. Aggressive nutritional interventions, including PEG tube feeding, may be necessary. Swallowing therapy should be intensified, and complications of radiotherapy (e.g., mucositis, xerostomia, fibrosis) must be actively managed. Endocrinology consultation may be beneficial in addressing the metabolic consequences of cancer cachexia.

Conclusion

This study reinforces existing evidence regarding symptom clusters in patients with HNC, particularly their associations with treatment types and comorbid conditions. The consistent clustering patterns suggest shared underlying mechanisms driving symptom burden. Our findings underscore the importance of integrating cluster-specific interventions into clinical practice. Future research with larger patient populations and advanced analytical tools is needed to further refine these clusters and develop personalized symptom management strategies to enhance patient quality of life.

Patient Consent

Informed consent has been taken from all the patients.

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Conflict of Interest

None declared.

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