

Symptoms and Problem Clusters in Cancer and Non-Cancer Patients in Specialized Palliative Care—Is There a Difference?

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Abstract

Context. In clinical practice, some symptoms and problems frequently occur in combination, which may have consequences for symptom management.

Objectives. Facing a growing number of non-cancer patients in palliative care, this study aimed to differentiate symptom clusters in the non-cancer population from those in cancer patients.

Methods. Inpatient data from the German Hospice and Palliative Care Evaluation between 2007 and 2011 were used for a cluster analysis of a 16-item symptom and problem checklist. An agglomerative hierarchical method was chosen. Coefficients from distance matrix ranging between 0 and 1 were calculated to indicate the interrelationship of clustered symptoms.

Results. The analysis identified five clusters in cancer patients: 1) nausea and vomiting ($d = 0.000$); 2) anxiety, tension, and feeling depressed ($d = 0.125$); 3) wound care and disorientation/confusion ($d = 0.229$); 4) organization of care and overburdening of family ($d = 0.202$); and 5) weakness, tiredness, need for assistance with activities of daily living, and loss of appetite ($d = 0.207$). Five comparable clusters were identified in non-cancer patients: 1) nausea and vomiting ($d = 0.000$); 2) anxiety, tension, and feeling depressed ($d = 0.166$); 3) organization of care and overburdening of family ($d = 0.187$); 4) weakness and need for assistance with activities of daily living ($d = 0.139$); and 5) tiredness and loss of appetite ($d = 0.182$).

Conclusion. As symptom clusters do not significantly differ between cancer and non-cancer patients, specific frequent symptoms in non-cancer patients should be assessed. Identification of symptom clusters may help to target therapies and focus the use of medications to improve patients' quality of

Introduction

The majority of patients receiving specialized inpatient palliative care suffer from numerous and complex symptoms and problems caused by their advanced terminal illness. The relief of these symptoms is one key target of palliative and hospice care.¹ Although patient symptoms should be considered individually, single symptoms may be not only seen as isolated problems but integrated into groups of symptoms, the so-called clusters.² There has been a growing interest in the method of clustering symptoms during the last decades. Whereas 777 citations on the search term *cluster analysis* are found in PubMed in 1990, at least 7882 citations may be found in 2012. Clusters are defined as at least two or more related symptoms forming a stable and independent group from other symptom clusters.³

The existence of symptom clusters is clearly reflected in clinical practice, where some symptoms do often appear together, and these symptoms seem to have a special interdependence regarding their incidence. Statistically defined symptom clusters are identified using cluster analysis from large data sets. These data sets are obtained by systematic assessment of multiple symptoms.

Thus far, several experiences with symptom clustering in patients with advanced disease have been reported internationally. These analyses often use data from symptom assessment tools such as the Edmonton Symptom Assessment Scale (ESAS)⁴ but have significant drawbacks in identification of valid clusters because of the limited symptom content of the tools. The most common clusters found in cancer patients comprise, for example, fatigue and drowsiness supplemented depending on publication to decreased appetite, dyspnea, pain or nausea.^{5–8} Anxiety and depression were clustered and completed by pain or sleep problems/insomnia.^{5–11} Another cluster was found for pain and fatigue,^{9,12} and depression

and pain (complemented by anxiety).^{6,7,9} In addition, nausea and vomiting were allocated to clusters empirically^{9–11,13,14} and, in some research attempts, complemented by appetite loss.¹⁴ Comparable symptom clusters were found in a first analysis of patients suffering from non-cancer diseases.^{15,16} Within these clusters, there may be differences caused by methodological aspects⁹ such as study design, number of assessed symptoms, and definition of clusters¹⁷; different care settings of different countries¹⁸; or other factors. These statistically identified, but common, symptom clusters can be recognized easily from clinical practice in palliative and hospice care.

Caregivers of any profession might consider the whole set of symptoms and their adequate evaluation, diagnosis, and treatment if a patient currently suffers from just one of the representatives of the symptom cluster. Nevertheless, in clinical practice, a subgroup of patients will not have additional symptoms or only some of the symptoms within a cluster. Single symptoms do not function as sentinel symptoms within a specific cluster, as presence of one symptom does not necessarily mean that the other symptoms will be present.

The consideration of symptom clusters in individual patients is known to supplement information on quality of life and even patient prognosis¹⁵; for example, there is a correlation between lower quality of life and the incidence of the symptom cluster pain, depression, and anxiety.⁷ This indeed emphasizes the importance of analyzing common symptom clusters.

In research, using symptom clustering might help discover associations of different symptoms, although not causation, which also could be important for clinical practice and attempts to standardize treatment strategies for single symptoms and symptom clusters.

Until now, relevant end-of-life studies dealing with symptom clustering have concentrated on patients with advanced cancer in the very late

stages of their disease. However, facing a growing number of non-cancer patients and attempting to prepare for their best possible treatment in palliative and hospice care,^{19,20} there is a need to investigate and identify symptom clusters in these patient groups. Therefore, this study aims to explore and compare cluster analysis for cancer and non-cancer patients receiving inpatient palliative care. Free from preliminary assumptions, similarities and differences in symptom clusters are evaluated for clinical relevance and what these similarities and differences mean for symptomatic treatment at the end of life for both populations. To our knowledge, this is the first attempt to establish symptom and problem clusters in advanced non-cancer patients treated in palliative and hospice care settings.

Methods

Study Framework

Since 1999, the German Hospice and Palliative Care Evaluation (HOPE), a nationwide documentation system, has been conducted in yearly three-month evaluation periods. During these three months, national palliative and hospice care institutions, such as inpatient palliative care units, hospices, or specialized outpatient palliative care teams, register basic data on all consecutive patients receiving their care. These data are predominantly used for benchmarking and quality management of palliative care and for research purposes in Germany.^{21,22}

The documentation system includes core information on patients' personal data, their social and living situations, diagnosis and stage of disease, individual symptom and problem burden, current medication, multiprofessional care approaches, characteristics of the end of treatment, and teams' satisfaction with the course of treatment and care.

From 2007 to 2011, patients ($n = 2055$ to 2444) were registered from palliative care units, inpatient hospices, outpatient palliative care teams, inpatient palliative care consultation teams, outpatient physicians, nursing care teams, and other medical wards participating in this survey. For this analysis, only data from inpatient palliative care units were included.

Study Material and Data Sets: HOPE Symptom and Problem Checklist

During the development and validation process of the HOPE Symptom and Problem Checklist (HOPE-SP-CL), a list of frequent symptoms was constructed and evaluated in the HOPE yearly populations. The HOPE core documentation system includes a 16-item SP-CL comprising eight physical symptoms (pain, nausea, vomiting, dyspnea, constipation, weakness, loss of appetite, tiredness), two nursing problems (wound care, assistance with activities of daily living [ADL]), four psychological symptoms (feeling depressed, anxiety, tension, disorientation/confusion), and two social problems (organization of care, overburdening of family). These symptoms and problems are ranked by team members on a four-point verbal rating scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe) at the time of patient admission. The HOPE-SP-CL was validated in 2012 and analyses of reliability and validity showed satisfactory to good psychometric properties.²³ The data from this SP-CL comprise the central component of the statistical analyses reported here.

The analysis presented here solely used secondary evaluations of available, deidentified HOPE data from 2007 to 2011. None of the data included identifying, or potentially identifying, information. For this analysis, no additional data collection, patient involvement, or study measures took place.

Data Analyses and Statistics

These analyses used anonymous data from inpatient palliative care patients, which were documented in HOPE between 2007 and 2011, retrospectively. The program SPSS 19.0 for Windows (IBM Corporation, Armonk, NY) was used for statistical analysis. The cluster analysis was based on the severity of the symptoms and problems of the HOPE checklist. All symptoms and problems are weighted equally within the HOPE checklist and valued as primary patient complaints in palliative and hospice care. Therefore, all 16 items from the SP-CL were analyzed as symptoms in the cluster analysis. This technique classifies symptoms and problems into several groups in which items are related within each group, but dissimilar between groups.²⁴

An agglomerative hierarchical method was used, which first considers each symptom and problem according to its intensity level as a cluster consisting of one item. It then groups similar symptoms and problems together stepwise until a final cluster that contains all of the symptoms and problems is built. The cluster analysis uses the average linkage between groups and the squared Euclidean distance. Coefficients (d) from the distance matrix ranging from 0 (indicating a minimum distance) to 1 (indicating a maximum distance) were calculated to indicate the extent of interrelation of the clustered symptoms and problems and are presented in dendrograms. Coefficients are usually defined by interpreting the course of the lines in the dendrograms, and a coefficient of ≤ 0.250 was selected here to define the final clusters. This coefficient is little more rigorous compared with the approach of Walsh and Rybicki.¹⁰

For comparison of the cluster analysis of the different patient groups, all cases were coded as 1) cancer patients if the recorded diagnosis that led to palliative care treatment was a cancer disease independent from additional non-cancer diseases (e.g., patient with rectum carcinoma and hypertension is coded as a cancer patient) or 2) non-cancer patients if only non-cancer diagnoses were recorded (e.g., chronic heart failure, motor neuron disease, chronic obstructive lung disease). Patients with a documented primary non-cancer diagnosis and mixed additional non-cancer disease (e.g., primary cirrhosis of the liver and secondary prostate cancer) were excluded from the analysis to prevent systematic bias in group allocation. Each patient belonged to one of these patient groups, so that no case could be evaluated in more than one group.

Ethics Statement

According to the statement of the local ethics committee of the medical faculty of the Friedrich-Alexander-Universität Erlangen-Nürnberg, and because of the study plan, formal application for approval was not necessary. The research meets all applicable standards for the ethics of experimentation and research integrity.

Results

Demographic and Disease-Related Data of the Study Sample

A total of 6181 cancer and 560 non-cancer patients documented in HOPE at the time of admission to an inpatient palliative care unit between 2007 and 2011 were included in this analysis. Cancer patients most often had cancer of digestive (29.5%) or respiratory and intrathoracic organs (19.0%) and breast cancer (10.7%). Non-cancer patients suffered from diseases of the circulatory (25.0%), nervous (17.5%), respiratory (11.6%), or digestive (10.7%) systems (Table 1).

The three most common symptoms documented with moderate and severe symptom intensities were weakness (cancer 85.4%; non-cancer 86.9%), tiredness (cancer 68.9%; non-cancer 70.4%), and need for assistance with ADL (cancer 75.1%; non-cancer 88.3%) (Table 2).

A higher proportion of non-cancer patients were female (56.6%) than cancer patients (50.8%) ($P = 0.008$, χ^2 test). Non-cancer patients were on average older (mean 73.8 ± 13.8 years) ($P = 0.000$, t -test) than cancer patients (mean 67.7 ± 12.5 years); 75.3% of cancer and 89.3% of non-cancer patients had an Eastern Cooperative Oncology Group performance status of grade three or four ($P = 0.000$, χ^2 test). The duration of stay was longer in cancer patients (mean 13.9 ± 12.8 years) than in non-cancer patients (mean 12.7 ± 11.0 years) ($P = 0.062$, t -test). Finally, 33.4% of cancer and 41.1% of non-cancer patients died during an inpatient stay ($P = 0.003$, χ^2 test).

Cluster Analysis

The analysis identified five clusters in cancer patients: 1) nausea and vomiting ($d = 0.000$); 2) anxiety, tension, and feeling depressed ($d = 0.125$); 3) wound care and disorientation/confusion ($d = 0.229$); 4) organization of care and overburdening of family ($d = 0.202$); and 5) weakness, tiredness, need of assistance with ADL, and loss of appetite ($d = 0.207$) (Fig. 1).

Five comparable clusters were identified in non-cancer patients: 1) nausea and vomiting ($d = 0.000$); 2) anxiety, tension, and feeling depressed ($d = 0.166$); 3) organization of care and overburdening of family ($d = 0.187$); 4)

Table 1
Absolute and Relative Number (in %) of Patients Suffering from Cancer vs. Non-Cancer Primary Diagnoses

Cancer Patients (n = 6181)				Non-Cancer Patients (n = 560)			
Primary Diagnosis	ICD-10 Code	n	%	Primary Diagnosis	ICD-10 Code	n	%
Malignant neoplasms of digestive organs	C15–C26	1823	29.5	Diseases of the circulatory system	I00–I99	140	25.0
Malignant neoplasms of respiratory and intrathoracic organs	C30–C39	1173	19.0	Diseases of the nervous system	G00–G99	98	17.5
Malignant neoplasm of breast	C50	660	10.7	Diseases of the respiratory system	J00–J99	65	11.6
Malignant neoplasms of female genital organs	C51–C58	443	7.2	Diseases of the digestive system	K00–K93	60	10.7
Malignant neoplasms of male genital organs	C60–C63	389	6.3	Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified	R00–R99	48	8.6
Malignant neoplasms of urinary tract	C64–C68	337	5.4	Diseases of the genitourinary system	N00–N99	32	5.7
Malignant neoplasms of ill-defined, secondary, and unspecified sites	C76–C80	313	5.1	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	D50–D90	25	4.5
Malignant neoplasms, stated or presumed to be primary, of lymphoid, hematopoietic, and related tissue	C81–C96	288	4.7	Diseases of the musculoskeletal system and connective tissue	M00–M99	20	3.6
Malignant neoplasms of lip, oral cavity, and pharynx	C00–C14	206	3.3	Endocrine, nutritional, and metabolic diseases	E00–E90	18	3.2
Malignant neoplasms of eye, brain, and other parts of the central nervous system	C69–C72	173	2.8	Certain infectious and parasitic diseases	A00–B99	15	2.7
Melanoma and other malignant neoplasms of skin	C43–C44	128	2.1	Mental and behavioral disorders	F00–F99	13	2.3
Malignant neoplasms of mesothelial and soft tissue	C45–C49	127	2.0	Injury, poisoning, and certain other consequences of external causes	S00–T98	13	2.3
Malignant neoplasms of thyroid and other endocrine glands	C73–C75	55	0.9	Other diseases		11	1.9
Malignant neoplasms of bone and articular cartilage	C40–C41	34	0.5	Missing data		2	0.4
Other malignant neoplasms		8	0.1				
Missing data		24	0.4				
Total		6181	100	Total		560	100%

weakness and need of assistance with ADL (d = 0.139); and 5) tiredness and loss of appetite (d = 0.182) (Fig. 2).

Discussion

The careful and repeated assessment of symptoms and problems of patients receiving palliative care is of high relevance for individual symptomatic treatment and the measurement of therapeutic benefits. Symptom assessment allows for awareness of changes in individual symptom burden and treatment necessities and for overall quality assurance in palliative care. However, not only the recognition of single symptoms but the awareness of symptom and problem clusters could be important for clinical practice. Therefore, the authors performed a cluster analysis from a

16-item checklist that includes physical, nursing, psychological, and social symptoms and problems. Although it has not yet become routine to include psychosocial and nursing problems along with physical symptoms in cluster analyses with an oncology focus, including them is central to a multidimensional approach of palliative and hospice care, as these domains are considered equal to physical symptoms.

Clinical experience has shown that some symptoms often occur together. Statistical analysis of the clustering of symptoms is still controversial. The methodology reveals the conflict and discrepancies between clinically observed and statistically identified clusters. It should be carefully considered that statistical significance is not an indicator for mandatory clinical relevance and importance.¹⁷ Symptom

Table 2
Relative Number (in %) of Patients Suffering From None, Mild, Moderate, and Severe Symptom and Problem Intensity: Cancer (n = 6181) vs. Non-Cancer (n = 560) Primary Diagnoses

HOPE-SP-CL 2007-2011	Patient Group	Intensity of Symptoms and Problems (%)				
		None	Mild	Moderate	Severe	Missing Data
Pain	C	19.5	22.2	28.8	27.4	2.1
	N-C	30.5	21.4	22.5	19.3	6.3
Nausea	C	44.8	23.9	16.9	11.4	3.0
	N-C	59.8	17.5	10.0	5.5	7.2
Vomiting	C	66.0	13.4	10.8	7.1	2.7
	N-C	75.2	8.2	6.1	4.6	5.9
Dyspnea	C	42.9	22.2	17.4	15.1	2.4
	N-C	35.7	20.7	20.4	18.2	5.0
Constipation	C	35.8	24.3	21.2	14.1	4.6
	N-C	38.4	20.5	18.0	14.5	8.6
Weakness	C	1.8	10.1	29.5	55.9	2.7
	N-C	1.6	4.8	22.3	64.7	6.6
Loss of appetite	C	11.5	16.9	25.2	42.0	4.4
	N-C	15.2	13.0	16.1	42.1	13.6
Tiredness	C	6.4	20.8	32.6	36.3	3.9
	N-C	5.3	14.5	22.5	47.9	9.8
Wound care problems	C	60.6	15.3	10.8	7.0	6.3
	N-C	46.1	15.2	14.1	14.3	10.3
Need of assistance with ADL	C	6.2	15.1	25.8	49.2	3.7
	N-C	3.8	4.3	12.1	73.2	6.6
Feeling depressed	C	32.7	28.7	20.5	10.5	7.6
	N-C	33.0	19.5	18.4	11.1	18.0
Anxiety	C	26.7	29.4	23.9	13.2	6.8
	N-C	26.1	23.0	22.3	13.4	15.2
Tension	C	21.7	29.6	26.0	15.6	7.1
	N-C	19.1	26.4	24.1	17.2	13.2
Disorientation/confusion	C	62.8	14.9	9.8	7.3	5.2
	N-C	41.8	13.6	11.4	17.3	15.9
Problems with organization of care	C	26.0	18.1	23.1	26.3	6.5
	N-C	25.9	14.3	16.4	31.8	11.6
Overburdening of family	C	14.6	18.8	25.3	33.4	7.9
	N-C	12.5	16.8	21.6	37.5	11.6

HOPE-SP-CL = HOPE Symptom and Problem Checklist; C = cancer; N-C = non-cancer; ADL = activities of daily living.

clustering completely relies on statistical allocations of symptoms without taking relevant clinical observations into account. Additionally, the number and selection of symptoms and problems assessed and used in the cluster analysis systematically influence the production and constellation of clusters, which then can vary in different investigations. Even though symptoms and problems are clustered similarly in cancer and non-cancer patients in the analysis presented here, this finding is of high clinical relevance. No matter what underlying disease causes a certain symptom for the patient, other symptoms and problems might likewise occur. Therefore, the symptom and problem burden during the terminal phase might be comparable in both cancer and non-cancer patients. For this reason, the comparable clustering of 1) nausea and vomiting; 2) anxiety, tension, and feeling depressed; and 3) organization of care and overburdening of family in both

cancer and non-cancer patients is intuitively obvious. The joint (non-)occurrence of these symptoms is evident in both clinical observations and in former research investigations.¹¹ Literature shows that in some trials loss of appetite was clustered with nausea and vomiting and clinically valid, but could not be replicated with the data reported here.^{25,26} These discrepancies in cluster findings also may derive from different methodological understandings and definitions of clusters as pairs or even more than two symptoms as a complex.²⁷ This underlines the clinical relevance and importance of statistically verified symptom clusters. Symptoms such as weakness and need for assistance with ADL seem to be clustered together self-evidently in non-cancer patients, as one might result from the other symptom. Increasing weakness may be accompanied by an increasing need for assistance with ADL, so that one symptom could be replaced by the other. These two

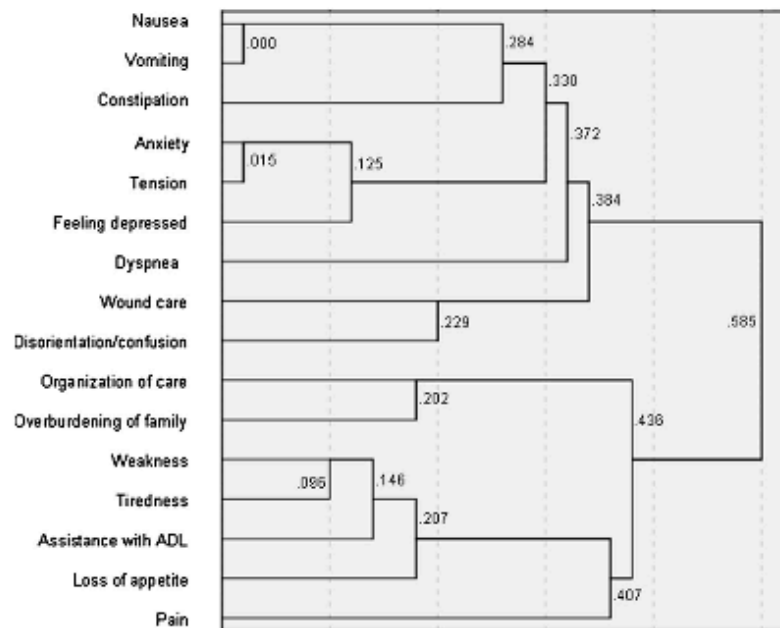


Fig. 1. Dendrogram of symptom clustering in cancer patients ($n = 6181$), displayed with distance matrix coefficients.

symptoms were complemented by another symptom cluster consisting of loss of appetite and tiredness, as found by Walsh and Rybicki.¹⁰ These four symptoms were recognized as one broader cluster in cancer patients. All in all, a similar picture is shown.^{7,8}

Surprisingly, pain was not clustered closely to any other symptom, both in cancer and non-cancer patients. From the literature,^{12,28} it was suggested that pain might be clustered with tiredness as it is known to cluster with fatigue or constipation.^{9,17,29} This finding could

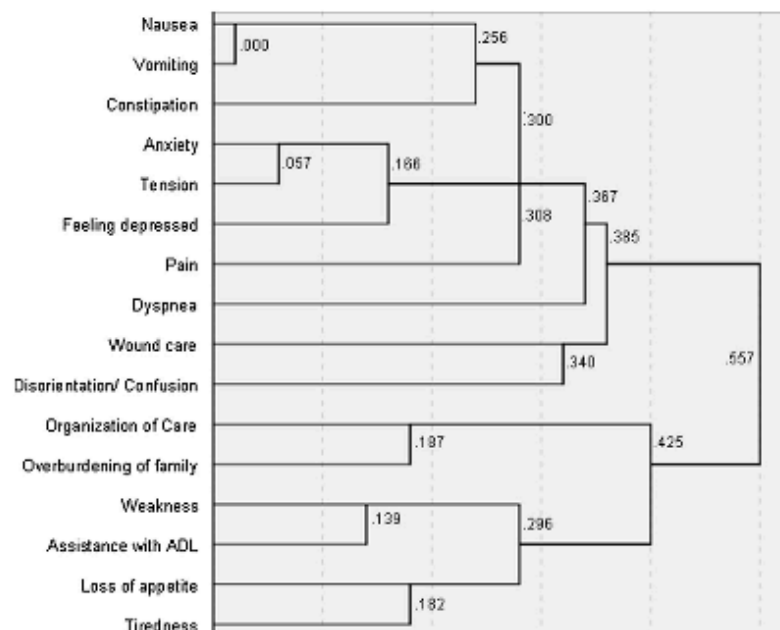


Fig. 2. Dendrogram of symptom clustering in non-cancer patients ($n = 560$), displayed with distance matrix coefficients.

not be replicated from the existing data in our study. The authors also hypothesized from clinical experience that dyspnea and anxiety might cluster together. It has been observed that the occurrence of dyspnea might aggravate anxiety and, in turn, increasing anxiety may aggravate dyspnea, in a vicious circle.^{30,31} However, this hypothesis could not be verified from the study data.

Symptoms and problems from the four HOPE subscales (physical, psychological, nursing, and social symptoms and problems) are not mixed in clusters. Overall, the clustering of symptoms and problems rather reflects the differentiation of the subscales within the HOPE-SP-CL. The clusters most often summarize physical, psychological, nursing, or social symptoms as it is intended and proven by the construct validity of the HOPE-SP-CL.²³

Significant differences and deviations between the cluster allocations could not be found. The symptom and problem clustering in cancer and non-cancer patients appears rather similar. Here the clustering of weakness and need for assistance with ADL as well as tiredness and loss of appetite in (non-)cancer patients emphasized the progression and advanced stages of disease in patients receiving inpatient palliative care in Germany. This also is displayed in the demographic data of this study such as even worse Eastern Cooperative Oncology Group performance status grades, older age, and a higher percentage of deaths in non-cancer patients at the end of treatment than in cancer patients.

Most likely, the same pathophysiology of single symptoms leads to the occurrence of other symptoms in a cluster that might be independent from the underlying primary disease. Therefore, symptoms might occur together no matter what disease the patient is suffering from.

Caregivers might gain additional insights into correlations of symptoms and problems and adapt and target therapeutic measures to whole complexes of symptoms and problems instead of single symptoms. Likewise, patients may benefit directly from recommendations from these findings.

Study Limitations

Although the framework of HOPE allowed for a very high number of data sets on

inpatient palliative care patients in Germany from the last several years, this investigation is based on a secondary analysis of prospective records of symptoms and problems and was not performed as a prospective study in particular. A prospective study would not have allowed for this extensive symptom clustering comparing cancer and non-cancer patients.

The symptom clustering presented here only considered data on patients treated in inpatient palliative care units. Therefore, the results may not be generalized to patients from different care settings such as outpatient palliative care or hospice.

The vast majority of patients included in the HOPE data suffered from cancer, but a considerable smaller proportion of patients were diagnosed with non-cancer diseases. Therefore, both populations cover a wide range of different cancer diagnoses or different neurologic, cardiac, pulmonary, and renal diseases in non-cancer patients. Accordingly, the results may be different for more homogeneous patient groups, both in cancer and non-cancer populations. Non-cancer patients may suffer more often and intensively from other symptoms and problems than cancer patients do. Patients suffering from neurologic diseases may have terminal symptoms such as dysphagia or spasticity,³² and patients with cardiac diseases may have edema more often than cancer patients,³³ whereas cancer patients may suffer more often and intensively from such problems as cachexia than non-cancer patients.³⁴ Unfortunately, these items are not included in the HOPE-SP-CL.

The cluster analysis depended directly on the set of symptoms and problems documented in HOPE. The data are limited by the fact that the SP-CL contains a finite number of symptoms and problems. The allocation of clusters may be very different when considering and including other symptoms and problems. Nevertheless, some symptoms were often clustered together in other research studies, so that a high validity of the clusters can be assumed.

The data collected involved physician-assessed symptoms and not patient-related assessment. This could potentially produce different clusters because physician-related assessment is likely to be distinctly different from patient-related assessment. Therefore, the comparison of symptom clustering from

staff and patient assessment would be preferable. In addition, the team members' ratings are overall impressions and do not consider precisely how often patients experienced these symptom and problem intensities. Unfortunately, many patients receiving inpatient palliative care are too impaired to take part in a comprehensive symptom self-assessment.

Conclusions

Five clusters were identified in cancer patients: 1) nausea and vomiting; 2) anxiety, tension, and feeling depressed; 3) wound care and disorientation/confusion; 4) organization of care and overburdening of family; and 5) weakness, tiredness, need of assistance with ADL, and loss of appetite. Five comparable clusters were identified in non-cancer patients: 1) nausea and vomiting; 2) anxiety, tension, and feeling depressed; 3) organization of care and overburdening of family; 4) weakness and need of assistance with ADL; and 5) tiredness and loss of appetite. In general, the identification of symptom clusters may help clinicians recognize symptoms and problems and target treatment accurately. This may lead to a focused use of medication and could directly improve patients' quality of life.³⁵ As symptom clusters do not significantly differ between cancer and non-cancer patients, specific frequent symptoms in non-cancer patients should be assessed according to the checklist. Further research on specific symptom characteristics in non-cancer patients might lead to additional insights; more evidence for defining symptom clusters will require additional longitudinal studies.

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