

Symptom Clusters and Quality of Life in Survivors of Lung Cancer

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Purpose/Objectives: To explore the prevalence and intensity of depression, fatigue, and pain in survivors of lung cancer; to examine the relationship of symptoms in a cluster; and to examine the relationship of the symptom cluster to quality of life (QOL).

Design: Secondary data analysis.

Setting: Online lung cancer support group.

Sample: 51 patients diagnosed with lung cancer.

Methods: Mailed survey with self-report of depression, fatigue, and pain measured by subscales of the Short-Form 36 Health Status Survey and QOL measured by the Fox Simple QOL Scale. Pearson's correlation and multiple regression analyses were used to examine the possible symptom cluster.

Main Research Variables: Depression, fatigue, pain, and QOL.

Findings: Depression, fatigue, and pain were found in a majority of survivors, with pain being the least common symptom. Fatigue was the most intense of the three symptoms. Two significantly correlated symptoms were depression and fatigue. The cluster explained 29% ($p < 0.01$) of the variance in QOL in the lung cancer survivors.

Conclusions: The data provided preliminary support for the presence of a symptom cluster in patients with lung cancer consisting of depression and fatigue. The cluster had a negative relationship with QOL. Survivors of lung cancer have depression and fatigue that affect QOL.

Implications for Nursing: Healthcare providers must assess the potential for symptoms to cluster, adversely affecting key patient outcomes such as QOL. Through increased knowledge of symptom clusters, clinicians will be able to more effectively target the most distressing set of symptoms for intervention.

Patients with lung cancer experience a variety of distressing symptoms, many of which begin prior to diagnosis and continue throughout the course of the disease and its treatments, adversely affecting functional status and quality of life (QOL). Treatment-related symptoms may exacerbate disease-related symptoms and further contribute to poorer QOL outcomes well into survivorship. Subjective symptoms such as depression, fatigue, and pain are common among all patients with cancer, including those with lung cancer, but often are underdiagnosed by clinicians, particularly once patients complete active treatment. Patients with lung cancer may experience a disproportionate level of symptom burden from diagnosis until death as compared to patients with other types of cancer (Cooley, 2000; Gift, Jablonski, Stommel, & Given, 2004). Part of the symptom burden experienced by patients with lung cancer may be the result of the simultaneous occurrence of symptoms, also known as "clustering" of symptoms.

Although clinicians long have noted that symptoms in cancer may occur together, research related to the clustering of symptoms in lung cancer is a relatively new area of investigation.

Key Points . . .

- ▶ Lung cancer survivors experience distressing symptoms that occur simultaneously.
- ▶ Symptoms that occur together may have a synergistic effect on each other and on key patient outcomes such as quality of life (QOL).
- ▶ Depression and fatigue were significantly related to each other in this study of lung cancer survivors.
- ▶ Depression and fatigue explain a significant amount of changes in QOL in lung cancer survivors and form a symptom cluster as defined by Kim, McGuire, Tulman, and Barsevick (2005).

Because individual symptoms of lung cancer are associated with decreases in QOL (Cella et al., 2005), assuming that clusters of symptoms might have an even greater effect on QOL is logical. Therefore, the purpose of this secondary data analysis was to explore possible symptom clusters in patients with lung cancer and their relationship to QOL. The specific aims were to explore the prevalence and intensity of subjective symptoms such as depression, fatigue, and pain in people surviving lung cancer; examine the relationship of simultaneously occurring or clustered symptoms with each other; and examine the relationship of the symptom cluster to QOL.

Theoretical Perspectives on Symptom Clusters

The theory of unpleasant symptoms suggests that symptoms cluster together, reinforce each other, and, as a result, influence outcomes such as QOL (Lenz, Pugh, Milligan, Gift, & Suppe, 1997). A symptom is defined as a "subjective experience reflecting the biopsychosocial functioning, sensations, or cognition of an individual" (Dodd, Miaskowski, & Paul, 2001, p. 466). Symptoms are multidimensional and can include perceptions of prevalence, intensity, and distress (Lenz

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et al.). Prevalence is defined as the frequency of a symptom. Intensity refers to the severity or amount of the symptoms being experienced. The current study describes the prevalence and intensity in a sample of lung cancer survivors.

Symptom cluster is a relatively new concept with a working definition suggesting that symptom clusters are composed of at least two (Kim, McGuire, Tulman, & Barsevick, 2005) or three interrelated symptoms (Dodd, Miaskowski, & Lee, 2004). For example, depression and fatigue or pain, fatigue, and sleep disturbance might constitute clusters if they are significantly correlated with each other. Work in the area is still preliminary, and guidance as to whether two or three symptoms are needed to constitute a cluster is yet to be determined. Few data support these theoretical suppositions, and only a small number of published studies are available in the literature for reference. The magnitude of correlation coefficients necessary to define a cluster also has not yet been determined.

In the theory of unpleasant symptoms, Lenz et al. (1997) proposed that symptom clusters have a resultant effect on important patient outcomes, such as QOL. The hypothesis was further supported by work by Dodd et al. (2004) and Kim et al. (2005). In the present study, QOL is defined as a subjective evaluation of an individual's current life circumstances as related to his or her culture, values (Haas, 1999), and life situation that ultimately results in a single evaluative outcome regarding the state of life for that individual. A subjective QOL scale with a summated score was used to measure QOL. With limited theoretical perspectives available, researchers also must turn to the empirical literature for guidance in study efforts in this important and emerging field.

Empirical Perspectives

Symptoms in Lung Cancer

The most common symptoms reported with all cancers, including lung cancer, are pain, depression, and fatigue (Cooley, 2000; National Institutes of Health [NIH] State-of-the-Science Conference Panel, 2002). As many as 90% of patients with cancer experience pain during the course of their illness (NIH State-of-the-Science Conference Panel). Fatigue also is quite common, particularly during treatment, and may affect 91% of those with cancer (Lawrence, Kupelnick, Miller, Devine, & Lau, 2004). Reports of incidence of depression in cancer are lower; however, at least 10%–25% of patients experience depression at some point during the course of cancer and its treatments. Depression is known to exacerbate pain and fatigue among individuals with cancer (Lawrence et al.; Meagher, Arnua, & Rhudy, 2001). Despite the incidence of these symptoms in patients with lung cancer, they have received limited study as a possible cluster in that patient population.

Symptom Clusters in Lung Cancer

Three published studies with the specific intent to explore the relationship among multiple symptoms in patients with lung cancer have been reported. Sarna and Brecht (1997) used factor analysis to explore symptom clusters in a study of 60 women diagnosed with lung cancer and found that symptoms could be clustered into four categories: physical and emotional suffering, respiratory distress, gastrointestinal distress, and malaise. In a sample of 112 people with newly diagnosed lung cancer (type not specified), with approximately one-

third undergoing some form of treatment, researchers found that seven symptoms were significantly correlated: fatigue, nausea, vomiting, weakness, poor appetite, weight loss, and altered taste (Gift, Stommel, Jablonski, & Given, 2003). The latter cluster is a mixture of signs and symptoms reflecting the disease-specific sequelae commonly associated with many cancers, including lung cancer. The clusters were identified at the time of diagnosis and were present at three and six months after diagnosis. In a third study of symptom clusters in 220 older adults with early-stage (38%) and late-stage (62%) lung cancer (type not specified), Gift et al. (2004) reported the same physical symptom cluster as in their 2003 study and found significant correlations among the number of symptoms, symptom severity, functional status, and health status.

Relationship of Symptom Clusters to Quality of Life in Patients With Lung Cancer

No studies to date have explored the influence of symptom clusters as currently defined in the literature by Dodd et al. (2004) and Kim et al. (2005) on the QOL of patients with lung cancer. However, several studies of symptoms in patients with lung cancer suggest that QOL is negatively associated with symptom distress. Sarna et al. (2002) found that depressed mood was associated with lower QOL in 142 people who had survived lung cancer for five years or longer. Sarna et al. (2004) later found that 142 disease-free lung cancer survivors reported that total symptom burden, rather than ventilatory impairment alone, contributed to decreased QOL. The studies provided an empirical basis that, when coupled with emerging theoretical perspectives on symptom clusters, indicates the need for examining the effects of symptom clusters on QOL in patients with lung cancer.

Methods

Design and Setting

This correlational study used secondary data from a convenience sample of 51 patients with lung cancer. The data set was obtained from a study focused on examining the psychometric properties of a new health-related QOL instrument (Fox, 2004). Patients were recruited from an Internet information and support group—the Association of Cancer Online Resources—using an advertisement that was approved by the human investigation committee at the researcher's university. Research suggests that using Internet-based research methods are efficacious (Jacobs, Bent, Tice, Blackwell, & Cumings, 2005; Kirsch & Lewis, 2004). Inclusion criteria for the original sample were (a) diagnosed with any type of lung cancer, (b) 18 years of age or older, (c) any race, and (d) able to read and speak English. Potential participants e-mailed the primary investigator to express interest in participating in the study. The investigator then obtained participants' mailing addresses and mailed a study packet, including a description of the study, study instruments, and a stamped, addressed envelope for the return of the study materials. The investigational review board of the researcher's university waived written consent in the study. Voluntary contact of the investigator by participants via e-mail, provision of a mailing address by participants, and return of the study packet were evidence of participants' consent. Patients were provided a consent form in the mailed study packet to assist in their decision to participate in the study. Fifty-one patients with lung cancer responded to

the advertisement and participated in the original study (N = 142), representing 36% of the total sample.

Instruments

The study packet contained an introductory letter, a demographic questionnaire, and three QOL questionnaires. The **demographic form** covered standard demographics of age, gender, type of cancer, stage of disease, treatment, and time since diagnosis. The **Short-Form 36 Health Status Survey (SF-36)** is a 36-item, multipurpose survey of general health status (Ware & Sherbourne, 1992). The SF-36 includes multi-item subscales to measure eight dimensions of health: physical functioning, role limitations, bodily pain, social functioning, general mental health, role limitations, vitality, and general health perceptions. Participants responded to symptom questions based on how they had been feeling during the prior four weeks so that reliance on long-term symptom memory was minimized. In the present study, the bodily pain subscale (two items) was used to measure pain, the mental health subscale (five items) was used to measure the degree of depressive symptoms, and the vitality subscale (four items) was used as a proxy measure for fatigue.

Given, Given, Azzouz, and Stommel (2001) used the subscales of the SF-36 to operationalize the measurement of pain and fatigue. The SF-36 has been tested extensively in thousands of patients with chronic physical and psychiatric disorders, including lung cancer (Handy et al., 2002; Sarna et al., 2002; Trippoli, Vaiani, Lucioni, & Messori, 2001). Alpha coefficients for internal consistency, reported as the median for 14 different studies, exceeded 0.80 for all subscales (Ware, Kosinski, & Gandek, 2004). Cronbach's alpha coefficient to estimate reliability was 0.086 for vitality and 0.87 for bodily pain for the subsample of 51 patients with lung cancer. Support for validity was obtained by multiple approaches, including factor analysis, criterion-related validity, and convergent validity (Ware et al.).

The **Fox Simple QOL Scale (FSQOLS)** is a 25-item scale to measure self-reported QOL (Fox, 2004). The instrument captures the cognitive and affective components of QOL. It contains no reference to symptoms; therefore, the threat of multicollinearity is minimized. Participants are asked to respond on a 5-point Likert-type scale to statements such as, "My life is good." Response options range from 1 (strongly disagree) to 5 (strongly agree). A total score is used; score range is 25–125, with higher scores indicating better QOL. The scale can be completed in five minutes or less. It has been tested in 142 patients with lung, ovarian, or colon cancer and 72 patients with various stages of brain cancer. Content validity of the scale was explored and supported using qualitative interviews from 14 participants with lung, colon, or ovarian cancer, who were a subgroup of the sample for the initial testing of the instrument. Psychometric evaluation of the FSQOLS included reliability estimation using alpha estimates (0.93) and item-factor correlations (0.40–0.86). For the subsample of 51 patients with lung cancer, the alpha coefficient was 0.93. The FSQOLS exhibited significant convergent validity coefficients with other popular QOL instruments, including the Ferrans and Powers (1985) QOL Index ($r = 0.70$, $p = 0.001$) and the General Well-Being Scale ($r = 0.61$, $p = 0.001$) by Dupuy (1984).

Analyses

Several analytic methods have been used to examine and validate symptom clusters in various patient populations,

including factor analysis (Gift et al., 2004; Sarna & Brecht, 1997), cluster analysis (Bender, Ergun, Rosenzweig, Cohen, & Sereika, 2005), multiple regression (Gaston-Johansson, Fall-Dickson, Bakos, & Kennedy, 1999), and multistage linear regression (Beck, Dudley, & Barsevick, 2005). None has been suggested as the best method to identify symptom clusters (Dodd et al., 2004). In the present study, regression was used to explain the interrelationships of a cluster of symptoms and QOL. Multiple regression is used to predict a continuous dependent variable (QOL) from a number of independent variables (symptoms in a cluster). Thus, for this study, multiple regression was an appropriate technique for determining the variance explained by individual and group symptom variables on a dependent outcome such as QOL. Using multiple regression, researchers can establish the relative predictive importance of the independent variables by comparing beta weights.

Cluster analysis is a method of analyzing relationships among variables and is used to classify similar cases into "like" groups, or clusters. Usually, cluster analysis is necessary when no a priori theoretical specification exists. Although cluster analysis may be appropriate when trying to identify a group of variables that have high degrees of association, it is not an appropriate technique for examining the relationship of a group of variables with a dependent variable. Although used previously, factor analysis was not considered an appropriate technique in the present study because of the structured symptom subscales of the SF-36 used in the original study.

To explore the interrelationships of symptoms (depression, pain, and fatigue) in patients with lung cancer, Pearson's correlations were obtained between mean scale scores for each symptom or set of symptoms. Scores were analyzed for number, pattern, and magnitude of correlation coefficients of symptoms to determine possible clusters. Multiple regression was used to examine the relationships between the individual symptom of interest and QOL to further define the cluster.

Results

Sample

A subset of 51 patients diagnosed with lung cancer was selected for analysis from the original data set consisting of a total of 142 patients with three common types of cancer (lung, colon, and ovarian). Participants ranged in age from 42–76 years ($\bar{X} = 56.9$ years, $SD = 7.85$), and most were Caucasian (98%), married (71%), and female (74%), with at least some college education (57%). The participants were diagnosed, on average, 32 months prior to the study and were distributed evenly among early stage (31% with stage I–II), late stage (35% with stage III–IV), and unknown stage of lung cancer (33%). Because the sample was recruited from the Internet, the researchers are unsure whether the participants truly did not know or had forgotten their stages of illness or whether they had unspecified stages of lung cancer. Clinically, some patients do know the type of cancer they have but not necessarily the stage. Ninety-four percent of the sample had undergone some form of treatment prior to the study: 50% had surgery, 37% underwent a combination of radiation and chemotherapy, and another 7% indicated "other" treatment. Other treatment was not defined by participants but may indicate they only had radiation or only had chemotherapy as compared to the combination of the two modalities.

Reported Prevalence and Severity of Symptoms

Subscale scores for the symptoms measured with the SF-36, including depression, fatigue, and pain, were calculated. Means, medians, and modes were calculated to describe the intensity of each symptom or set of symptoms. Frequencies and percentages for categorical variables, means, standard deviations, and medians are presented for continuous measures in Table 1. The reported symptoms are depression, fatigue, and pain. For the total symptoms examined in the study (depression, fatigue, and pain), 94% of patients reported having at least “a little bit” of all three symptoms, 98% reported depression, 100% reported fatigue, and 65% reported pain. Prevalence of symptoms was reported in this manner because the developers of the SF-36 do not provide or recommend symptom subscale cut-off points. The SF-36 symptom subscale scores are most typically interpreted by comparison against normed values.

The symptoms in the patient sample ranked according to severity were fatigue ($\bar{X} = 47$, scale = 0–100), depression ($\bar{X} = 73$, scale = 0–100), and pain ($\bar{X} = 74$, scale = 0–100), with lower scores indicating greater intensity of symptoms. Using one-sample *t* tests, additional analysis was done to compare the mean fatigue, pain, and depression scores of the sample with other normed samples reported in the SF-36 survey guide (Ware et al., 2004). Participants in the Ware et al. study had levels of pain and depression that were similar to those of a similar age group (55–64) of a healthy population ($N = 164$); however, the current study's sample had significantly greater fatigue ($t = -3.551$, $df = 50$, $p < 0.001$) than the healthy population. In further analysis, the sample in the current study was compared to a normed group of patients with chronic obstructive pulmonary disease because of the similarities in respiratory disease. Upon comparison, again using one-sample *t* tests, patients in the current study had similar high levels of fatigue ($t = 0.487$, $df = 50$, $p = 0.628$) but lower levels of depression ($t = 1.94$, $df = 50$, $p = 0.05$) and pain ($t = 5.55$, $df = 50$, $p < 0.001$).

Relationships Among Symptoms

Significant relationships were found among simultaneously occurring symptoms in the lung cancer subgroup as a whole ($N = 51$) (see Table 2). Among the 51 patients, depression was significantly correlated with fatigue ($r = 0.44$, $p = 0.01$) and fatigue was significantly correlated with pain ($r = 0.40$, $p = 0.01$).

Symptoms and Quality of Life

The 51 patients with lung cancer had a mean QOL score of 97.27 on the FSQOLS (score range for the scale is 25–125, with higher scores representing better QOL). Depression ($r = 0.51$, $p = 0.01$) and fatigue ($r = 0.38$, $p = 0.01$) were significantly correlated with QOL. Pain was not significantly correlated with QOL.

Table 1. Descriptive Statistics for Symptoms

Symptom	Prevalence n (%)	\bar{X}	SD	Median
Depression	50 (98)	73	18.1	76
Fatigue	51 (100)	47	23.0	50
Pain	33 (65)	74	24.5	75

$N = 51$

Table 2. Symptom Scale Score Correlations for All Patients With Lung Cancer

Symptom	Depression	Fatigue	Pain	Quality of Life
Depression	1.00	0.44*	0.114	0.510*
Fatigue	–	1.00	0.400*	0.380*
Pain	–	–	1.000	0.140
Quality of life	–	–	–	1.000

$N = 51$

* $p = 0.01$ (two-tailed)

Examining the Cluster

The researchers used SPSS® 13 (SPSS Inc., Chicago, IL) for Windows, to enter the two independent variables that were correlated with QOL in this sample (depression and fatigue) in a block and regress the variables on the dependent variable (QOL) to explore the existence of a cluster. The two variables explained 29% ($F = 9.80$, $p < 0.001$) of the variance in QOL. Then, hierarchical multiple regression analysis was conducted to examine the independent contribution of depression and fatigue on QOL scores. In the analyses, depression was highly significant ($F = 16.99$, $p < 0.001$), accounting for 26% of the variance in QOL, leaving fatigue with a minimal and insignificant contribution.

Discussion

Using the working definition of a symptom cluster proposed by Kim et al. (2005), the results of this secondary data analysis in relation to depression and fatigue supported the presence of a “symptom cluster” for the 51 patients with lung cancer. Kim et al. suggested that for a cluster to be defined, at least two symptoms should be significantly correlated and should have a relationship with an important patient outcome such as QOL. In the present study's sample, the cluster was comprised of depression and fatigue.

Although pain was significantly correlated with fatigue, it was not correlated with depression or QOL in this sample. Because multiple regression techniques are based on normally distributed data, variables that are not normally distributed and have nonlinear relationships with the dependent variable (e.g., pain in the current sample) have a regression coefficient that does not capture the extent of a curvilinear relationship.

It could be argued that pain and fatigue form a cluster merely by their significant correlation with each other, if correlation alone defines the cluster. However, in keeping with the theoretical underpinnings of the current study, because pain was not correlated with a key patient outcome (i.e., QOL), it was not considered part of the cluster and, therefore, not included in further analysis. Although pain has been identified as a component of a symptom cluster in patients with cancer in a previous lung cancer symptom study (Sarna & Brecht, 1997), in this analysis, pain was not correlated with either depression or QOL. Because pain was not normally distributed, making informed statistical inferences is difficult. Among participants with elevated pain scores, a moderate correlation with fatigue was found. However, many participants reported having no pain. Perhaps in this sample of patients—most who had completed active treatment—pain was less of a problem as a result of

a lower acuity of pain or accommodation to pain during the survivorship period. Further study of the relationship of pain to other symptoms and to QOL is indicated in patients with lung cancer across the illness continuum.

The cluster described in this study is somewhat difficult to compare to the three previous studies of symptom clusters in lung cancer because of the differences in the terminology used for different symptoms (malaise versus fatigue versus weakness), the scales used to measure the symptoms, and the methods used to determine the cluster. The differences are important and should be considered in future research involving symptom clusters in patients with lung cancer. However, the fact that this area of research is emerging demonstrates the importance of the findings from this analysis.

Important information also was revealed in this study related to the prevalence and severity of symptoms of lung cancer survivors. First, depression, fatigue, and, to a lesser degree, pain remain with patients with lung cancer well into the survivorship period, reflecting findings from previous studies such as Sarna et al. (2002) and Svobodnick et al. (2004). Overall, patients with lung cancer in this sample had relatively high QOL ($\bar{X} = 97$, scale range = 25–125), particularly in the face of fatigue levels that were significantly above norms for the same age group of those in a healthy population and similar to those living with chronic obstructive pulmonary disease. Some cancer survivors rate their QOL high, even in the face of significant symptom burden.

In summary, the current study revealed that depression and fatigue were significantly correlated with each other and with a key patient outcome, QOL. Although Gift et al. (2004) reported that a cluster was formed because of a significant relationship with functional and health status, the current study revealed a cluster that was significantly correlated with QOL and also found that the cluster explained the 29% variance in QOL in the overall lung cancer subgroup ($N = 51$). This is the first study to report the relationship of QOL to symptom clusters and lung cancer. Healthcare providers may underdiagnose depression, fatigue, and pain because they are subjective in nature. If these symptoms are common in lung cancer, then examining their relationship to each other and their effects on patient-reported outcomes such as QOL in all future studies involving this disease is critical.

Study Limitations

The use of a convenience sample obtained from an online cancer support group limits the conclusions based on this secondary data analysis. Although the data in the present study provide some indication that the identified symptom cluster is strongly related to decreased QOL, further study should include a larger sample to more fully describe the potential interactive effects of the dependent variables on QOL. Because pain was not a severe symptom in this sample, its relationship to QOL may have been attenuated. The sample may not have been representative of the population of patients with cancer because bias was introduced from being financially able to own a computer, using the Internet for information and support, and being almost exclusively Caucasian and highly educated. In addition, those who volunteered to participate may have been more motivated to do so, introducing self-selection bias. The time since diagnosis in the sample of patients with differing types of lung cancer

was 32 months, indicating that many who participated were survivors of lung cancer and not representative of the overall population of patients with lung cancer. Finally, the analytic strategies were limited by the use of a data set originally intended for a different purpose; therefore, the exploration of symptom clusters was limited. The small sample size is an additional limitation of the study and limits the generalizability of the data; a larger sample in the future will allow for more rigorous analysis.

Implications for Nursing

Healthcare providers must assess the simultaneous occurrence of symptoms and be aware of the potential for symptoms to cluster, possibly resulting in synergistically adverse effects on key patient outcomes such as QOL and functional and health status. Through increased knowledge of symptom clusters, clinicians will be able to more effectively target the most distressing sets of symptoms for intervention.

Cancer survivors need specialized care beyond the treatment phase of their illnesses. The findings of this study highlight that survivors of lung cancer are experiencing distressing symptoms, specifically depression and fatigue, well into cancer survivorship and that these clustered symptoms significantly influence QOL. Nurses and other healthcare professionals must take deliberate steps to assess for and intervene in depression and fatigue so they can assist patients in improving their QOL beyond the acute stage of illness and well into survivorship. If symptom cluster research is to become useful in practice, assessing—clinically and through research—the interventions that most effectively target all of the symptoms in a cluster or the one that is most powerful in altering outcomes will be critical.

Future Research

Future research exploring symptom clusters in patients with lung cancer is necessary to better manage symptoms in that patient population. As reported in this study, subjective symptoms such as depression and fatigue occur well into the illness trajectory of lung cancer and are significantly related to each other. Pain, although not identified as part of the cluster in these survivors of lung cancer, is likely a critical symptom in other subgroups of patients with lung cancer. Future studies must include all of these variables. Replication of the study with a larger sample is indicated to further examine the effects of symptom clusters on QOL and other clinical outcomes.

As more studies of symptom clusters are conducted, investigators will need to synthesize the existing body of symptom cluster work in lung cancer and integrate that work into their studies in a way that might allow comparison across studies. Because the current study was conducted from secondary data, it did not allow the integration and testing of symptoms that already have been identified as part of other clusters such as loss of appetite, nausea, vomiting, and respiratory signs and symptoms. Furthermore, clusters need to be compared across the illness continuum for those in the acute phase of disease versus those who are considered survivors.

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