*Original Article*

# Consensus in Identification and Stability of Symptom Clusters Using Different Symptom Dimensions in Newly Diagnosed Acute Myeloid Leukemia Patients Undergoing Induction Therapy

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## Abstract

**Context.** An unresolved issue in symptom cluster (SC) research is that the numbers and types of SCs vary based on the multiple dimensions of the experienced symptoms that are used for SC identification.

**Objective.** This study aimed to identify SCs using the ratings of occurrence, severity, and distress in newly diagnosed acute myeloid leukemia (AML) patients at three stages of their induction therapy (i.e., T1, T2, and T3). Then, we evaluated the consensus among the numbers and types of symptoms in each SC identified by multiple dimensions over time.

**Method.** The Chinese version of the Memorial Symptom Assessment Scale was used to evaluate the occurrence, severity, and distress ratings of 32 symptoms in patients newly diagnosed with AML during their induction therapy. Exploratory factor analysis was used for SCs identification.

**Results.** Using the three dimensions in the AML patients ($n = 126$), four SCs were identified at T1 and T3 and three SCs were identified at T2. The number of symptoms in individual SCs varied over time, whereas the specific symptoms in SCs remained similar over time. The severity ratings fit the data better than did the ratings of occurrence and distress.

**Conclusion.** These findings provided insights into the most common SCs in AML patients undergoing induction therapy by multidimensional evaluation and could lay the foundation for future targeted symptom interventions. Further studies are needed to explore the mechanisms of SCs in AML patients undergoing the chemotherapy. J Pain Symptom Manage 2019;57:783–792. 

***Key Words***

*Symptoms, symptom clusters, acute myeloid leukemia, induction therapy, exploratory factor analysis, symptoms occurrence, symptom severity, symptom distress*

## Introduction

Previous study has revealed that oncology patients commonly experience multiple symptoms due to their disease and/or treatment.[1] Symptom cluster (SC) was then proposed as a term to describe this phenomenon and was defined as "two or more symptoms coexistent in a stable group. It may reveal specific underlying dimensions of symptoms and relatively independent of other clusters. Relationships among symptoms in a cluster are usually stronger than relationships among symptoms across different clusters."[2] This may reveal specific underlying mechanism of the symptoms. Symptoms in a cluster may grievously increase symptom burden and synergistically affect

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cancer patients' outcomes such as functional status and quality of life.[3-5]

However, many questions remain unanswered in the evaluation of SCs. One question is "If the evaluation scale contains multidimensional items, what dimension fits the data best for identifying SCs?" For example, the Memorial Symptom Assessment Scale (MSAS) is widely used to assess the symptoms experience of cancer patients based on three dimensions (i.e., occurrence, severity and distress).[6] Baggott et al.,[7] Wong et al.,[8] and Sullivan et al.[9] all used symptom severity ratings and occurrence ratings to identify SCs among homogeneous cancer patients (in pediatric oncology ($n = 131$), lung cancer ($n = 145$), and breast cancer ($n = 515$), respectively.). Their results showed that both the numbers and types of SCs were relatively similar between the two dimensions. By contrast, Kim et al.[10] found higher consensus of SCs identified by using severity ratings than of those identified by using occurrence ratings in breast cancer and prostate cancer patients ($n = 160$). Only one study has used severity ratings and distress ratings to identify and compare SCs in breast cancer patients and the results showed similar consensus between the two dimensions ($n = 320$).[11]

Another important area in SC research is to evaluate the stability of SCs over time. To date, only one longitudinal study has focused on researching the trajectory of SCs in breast cancer patients undergoing chemotherapy using occurrence ratings and severity ratings ($n = 540$). The results showed that five of eight SCs were quite stable across two dimensions (i.e., psychological, hormonal, nutritional, gastrointestinal, and epithelial).[12] However, no study has focused on evaluating the stability of SCs using the ratings of occurrence, severity, and distress.

To date, many studies have focused on SCs identification in breast, lung, and prostate cancer patients, among others, whereas inadequate attention has been paid on hematological malignancies. Leukemia is one of the most common hematological malignancies. In 2015, in China, the incidence rate of leukemia was 75.3 per 100,000 and the mortality rate was 53.4 per 100,000. Acute myeloid leukemia (AML) is the most common leukemia in adults. It causes bone marrow failure and tissue infiltration.[13-16] Newly diagnosed AML patients first receive induction therapy to achieve complete remission. However, it can increase the number and severity of unpleasant physical and psychological symptoms, such as worrying/sadness, fatigue, and pain, among others, and these symptoms can be coexistent.[17,18] Studies on SC identification in AML patients undergoing induction chemotherapy are limited. Our literature search has shown only one study that identified SCs by occurrence ratings in adolescent and child patients and part of them had been diagnosed with leukemia (35.2%).[19]

To care for this patient group effectively, their symptoms experience needs to be understood. Identification of SCs using the ratings of occurrence, severity, and distress and evaluation of consistency of these SCs will lay the foundation for the future targeted symptom interventions in AML patients.

## Materials and Methods

### Patients and Settings

This study was observational, which longitudinally evaluated the symptom experience of AML patients during their induction therapy. The study was conducted from 1st March 2017 to 31st August 2018 in the hematology unit of a tertiary hospital affiliated with a medical university in PR China.

Convenience sampling of AML patients who were admitted to the unit for their induction therapy (seven days of continuous infusion of cytarabine plus further three days of anthracycline infusion was performed to recruit study participants). The inclusion criteria for the participants were as follows: 1) newly diagnosed with AML, 2) received their induction regimen, 3) aged from 18 to 60 years, and 4) able to understand Chinese. The exclusion criteria included the following: 1) deterioration in clinical condition and 2) cognitive or psychosis impairment identified from their medical record.

### Instrument

A self-designed demographic questionnaire was used to obtain information on participants' age, gender, marital status, and education. Clinical characteristics, such as body mass index and status of organ infiltration, were obtained from the patients' medical record.

The Karnofsky Performance Status Scale was used by the clinicians to assess the physical function of patients. This scale is an 11-point rating scale from 0 (dead) to 100 (normal function).[20,21]

MSAS is a comprehensive self-reporting questionnaire designed to assess the multidimensional experience of 32 symptoms.[6] During the assessment, each patient was asked whether he or she had experienced the symptoms presented in the scale during the previous week (occurrence). If "yes," the patient was then requested to rate the severity and distress of each symptom. Symptom severity was measured using a four-point Likert scale (1 = slight, 2 = moderate, 3 = severe, 4 = very severe), and a five-point Likert scale (0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, 4 = very much) was used to measure the symptom distress. The Chinese version of the MSAS (Ch-MSAS) was tested previously showing adequate validity and reliability in the local settings (Cronbach's alpha from 0.79 to 0.87).[22]

*Study Procedures*

The study was approved by the Research Ethics Committee of Nanfang Hospital (NFEC-2017-187). Before data collection, the researchers explained the study purposes and procedures to all eligible patients. Then, the researchers assured the potential patients that their personal and medical information would be stored confidentially and reported anonymously. After written consent was obtained from the patients, they were requested to complete the questionnaires in the hospital. For the patients who were too weak to complete the questionnaires, the researchers obtained the information by reading the items to the patients.

The study collected data over 21 consecutive days around the induction therapy. These days were divided into three stages: −6 to 0 days before chemotherapy (T1); +1 to +7 days during chemotherapy (T2); and +1 to +7 days after chemotherapy (T3). The researcher collected the data at fixed time because symptoms fluctuate within a cycle of chemotherapy.

*Statistical Analyses*

The data were analyzed using the Statistical Package for the Social Sciences, version 22.0 (SPSS, IBM, New York) for Windows. Descriptive statistics and frequency distributions were calculated for the patients' demographic information, clinical characteristics, and symptom occurrence. The ratings of severity and distress were presented as the mean values with their SDs. A *P*-value of $<0.05$ was considered significant.

The selection of symptoms was based on the occurrence ratings, whereas the composition of SCs was based on the ratings of occurrence, severity, and distress. The occurrence ratings of the symptoms that appeared in >20% and <80% of the patients were included in the analyses for the purpose of providing enough variation and covariation in the data to perform the exploratory factor analysis (EFA).[7-12] EFA was used to create the numbers and types of SCs because EFA can identify the relationships among observed variables that can be explained by many latent and unobserved variables (i.e., factors).[23]

The severity ratings were estimated to include a zero (i.e., 0, 1, 2, 3, 4) in the EFA analysis because if so, the pairwise missingness (i.e., 1-covariance coverage for each of the item pairs) would be over 90% and the estimation failed to converge.

For the EFA, a factor was adequately defined as an SC if at least two items (symptoms) had factor loading (i.e., structure coefficients following rotation) ≥0.4.[23] In our study, the occurrence item was evaluated as dichotomous and tetrachoric correlations were used to create the matrix of associations. The severity and distress items were evaluated as ordinal, and polychoric correlations were used to create the matrices of associations. The method of unweighted least squares with geomin (i.e., varimax) rotation was conducted to estimate the configuration of occurrence, severity, and distress. The geomin rotation method can identify the best fit for the model because it improves both the factor correlation and the factor solution interpretability. The unweighted least squares estimator was applied because it can increase the reliability of the results for Ch-MSAS items containing dichotomous and ordinal items.[24,25]

Factor solutions were estimated from two to five factors. The factor solution with the greatest interpretability and clinical meaningfulness was selected as it met the criteria inclusion for evaluating simple structure (i.e., size of item loadings and number of items on a factor). Then, each SC was named based on the predominant symptoms in the cluster.

To evaluate the agreement of each SC across the multiple dimensions, we applied the criterion that at least 75% agreement of the symptoms within a cluster should be presented, including prominent and important symptoms. The percentage agreement of symptoms among SCs was calculated using the following formula[26]:

The percentage agreement (%) = the total number of symptoms based on one dimension in an SC/the total number of symptoms based on the multiple dimensions × 100%.

## Results

*Demographic and Clinical Characteristics*

Of the 201 eligible AML patients approached, 168 (84%) consented to participate. Of these, 126 (63%) completed the three questionnaires and were finally included in the analysis. A flow diagram of patient inclusion and exclusion is shown in Fig. 1.

The demographic and clinical characteristics of the patients are displayed in Table 1. The sample was 56.3% females and 70.6% were married with a mean age of 35.44 (SD = 11.56) years. Their mean body mass index score was 21.78 kg/m$^2$ (SD = 3.64). Nearly all of them were free of organ infiltration (93.7%). The Karnofsky Performance Status Scale scores were 62.30 (SD = 18.5), 41.98 (SD = 13.21), and 44.81 (SD = 15.10) at T1, T2, and T3, respectively.

*Symptom Occurrence, Severity, and Distress Rates*

As shown in Table 2, 14 (T1), 19 (T2), and 24 (T3) symptoms with occurrence ratings present in >20% and <80% of patients were included in the EFA. Worrying was the highest occurrence ratings across the three dimensions (96.0%, 93.7%, and 94.4%, respectively).

*Symptom Clusters Based on Occurrence Ratings Over Time*

As presented in Table 3, the EFA of the dichotomous symptom occurrence ratings showed that three-, two-, and four-factor solution (SCs) yielded the best fit with the data at T1, T2, and T3, respectively. The SCs of nutritional (i.e., cough, dry mouth, sweats, lack of appetite, and change in the way food tastes), sickness behavior (i.e., difficulty sleeping, shortness of breath, feeling sad, dizziness, and change in skin), and neuropathy (i.e., difficulty concentrating and feeling drowsy) were identified at T1. Gastrointestinal (i.e., difficulty concentrating, nausea, and vomiting) and psychological (i.e., feeling nervous, difficulty sleeping, shortness of breath, and feeling sad) were identified at T2. Nutritional (i.e., dry mouth, mouth scores, and constipation), gastrointestinal (i.e., difficulty concentrating, nausea, vomiting, feeling drowsy, and "I do not like myself"), psychological (i.e., feeling nervous and feeling sad), and body image (i.e., itching and change in skin) were identified at T3. The factor solutions explained 32.64%, 19.80%, and 21.16% of the total variance at T1, T2, and T3, respectively.

*Symptom Clusters Based on Severity Ratings Over Time*

The EFA of the ordinal symptom severity ratings indicated that four-, three-, and four-factor solution (SCs) yielded the best fit to the data at T1, T2, and T3, respectively (Table 3). The SCs of nutritional (i.e., couth, dry mouth, and sweat), sickness behavior (i.e., difficulty sleeping, shortness of breath, and feeling sad), neuropathy (i.e., difficulty concentrating and feeling frowsy), and body image (i.e., itching and mouth scores) were identified at T1. Sickness behavior (i.e., difficulty concentrating, change in the way food tastes, and "I don't like myself"), gastrointestinal (i.e., difficulty concentrating, nausea, vomiting, and change in the way food tastes), and psychological (i.e., feeling nervous, difficulty sleeping, and feeling sad) were identified at T2. Nutritional (i.e., dry mouth, change in the way food tastes, mouth scores, weight loss, constipation, and "I do not like myself"), gastrointestinal (i.e., difficulty concentrating, nausea, vomiting, and feeling drowsy), psychological (i.e., feeling nervous, difficulty sleeping, feeling sad, and feeling irritable), and body image (i.e., itching and

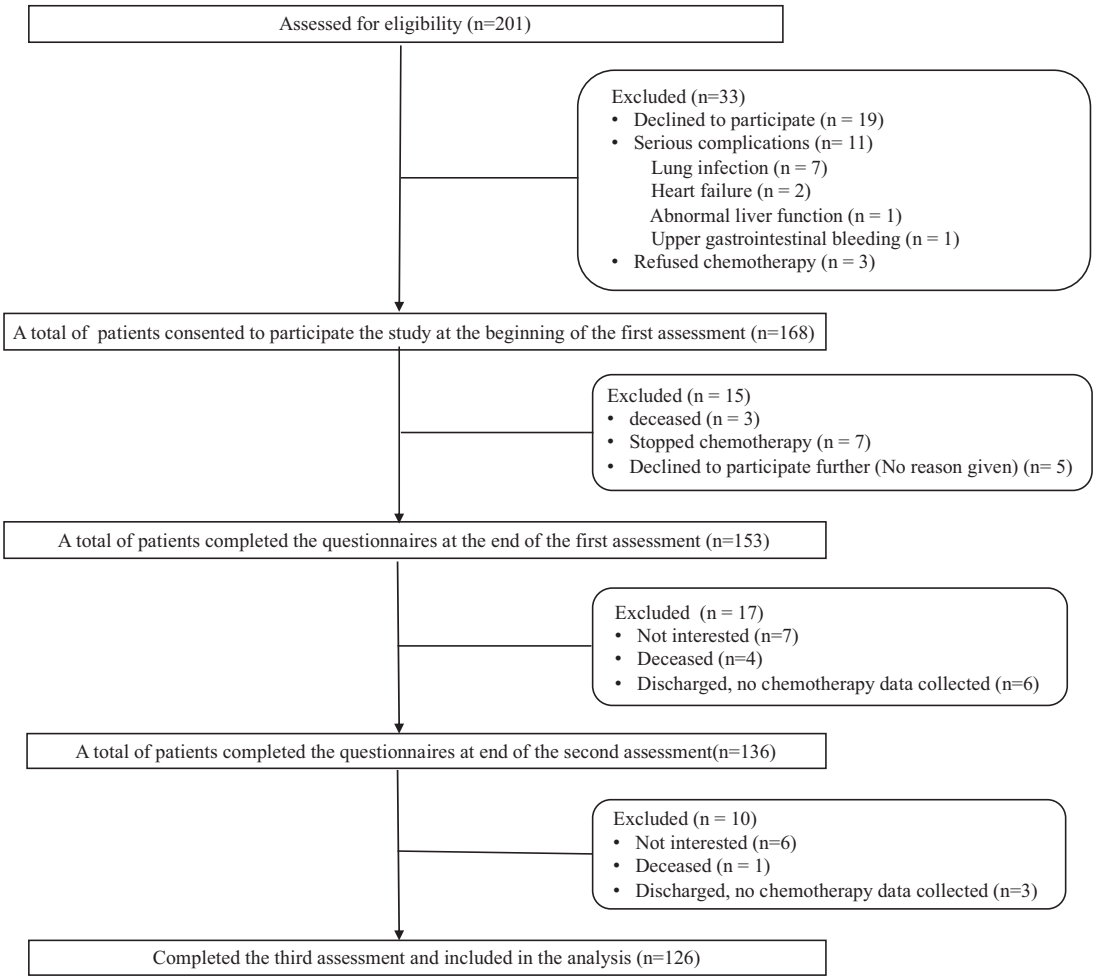


Fig. 1. Flow diagram of participant recruitment.

*Table 1*
**Demographic and Medical Characteristics of Newly Diagnosed Acute Myeloid Leukemia Patients Undergoing Chemotherapy ($N = 126$)**

| Characteristic | Mean (SD) | Range |
|---|---|---|
| Age (yrs) | 35.44 (11.56) | 18.0–59.0 |
| Body mass index (BMI kg/m$^2$) | 21.78 (3.64) | 15.1–36.7 |
| KPS | | |
| T1 | 62.30 (18.51) | 10–90 |
| T2 | 41.98 (13.21) | 10–70 |
| T3 | 44.84 (15.10) | 20–90 |
| | Category | *n* (%) |
| Gender | Male | 71 (56.3) |
| | Female | 55 (43.7) |
| Marital status | Single | 34 (27.0) |
| | Married | 89 (70.6) |
| | Divorced | 3 (2.4) |
| Education | High school or below | 79 (62.7) |
| | College | 47 (37.3) |
| Organ infiltration | None | 124 (98.4) |
| | Central nervous system | 2 (1.6) |

SD = standard deviation; T1 = -6 to 0 days before chemotherapy; T2 = +1 to +7 days during chemotherapy; T3 = +1 to +7 days after chemotherapy.

changes in skin) were identified at T3. The factor solutions explained 37.85%, 27.06%, and 32.92% of the total variance at T1, T2, and T3, respectively.

### *Symptom Clusters Based on Distress Ratings Over Time*

The EFA of the ordinal symptom distress ratings indicated that four-, three-, and four-factor solution (SCs) yielded the best fit to the data at T1, T2, and T3, respectively (Table 3). The SCs of nutritional (i.e., cough, dry mouth, and sweats), sickness behavior (i.e., shortness of breath, feeling sad, and change in skin), neuropathy (i.e., difficulty concentrating, feeling drowsy, and feeling irritable), and body image (i.e., itching and mouth scores) were identified at T1. Sickness behavior (i.e., difficulty concentrating, change in the way food tastes, and "I don't like myself"), gastrointestinal (i.e., difficulty concentrating, nausea, vomiting, and change in the way food tastes), psychological (i.e., feeling nervous and feeling sad) were identified at T2. Nutritional (i.e., dry mouth, change in the way food tastes, difficulty concentrating, constipation, and "I don't like myself"), gastrointestinal (i.e., difficulty concentrating, nausea, vomiting, and sweats), psychological (i.e., feeling nervous and feeling sad), and body image (i.e., itching and changes in skin) were identified at T3. The factor solutions explained 34.62%, 25.90%, and 32.50% of total variance at T1, T2, and T3, respectively.

### *Consensus of SCs Based on the Three Dimensions Over Time*

At shown in Table 3, the numbers and agreement of symptoms contained in each SC based on the three dimensions varied over time. At T1, a total of five symptoms were included in both the nutritional (i.e., 100%, 60%, and 40% agreement) and the sickness behavior (i.e., 100%, 60%, and 60% agreement) using the three dimensions. Three symptoms were included in the neuropathy (i.e., 66.7%, 66.7%, and 100% agreement). Two symptoms were included in the body image (100% agreement) using ratings of severity and distress.

At T2, a total of three symptoms were included in the sickness behavior by the ratings of severity and distress (both 100% agreement), whereas four symptoms were included in each of the gastrointestinal (75.0%, 100%, and 100% agreement) and the psychological (i.e., 100%, 75%, and 50% agreement) using the three dimensions.

At T3, a total of seven symptoms were included in the nutritional (i.e., 42.9%, 85.7%, and 71.4% agreement), six were included in the gastrointestinal (i.e., 83.3%, 66.7%, and 66.7% agreement), four were included in the psychological (i.e., 50.0%, 100%, and 50.0% agreement), and two were included in the body image (all 100% agreement) by using the three dimensions.

## *Discussion*

To our knowledge, this is the first study to identify SCs that based on the ratings of occurrence, severity, and distress in newly diagnosed AML patients undergoing induction therapy, and then to compare their stability among the three dimensions over time. Our results demonstrated that the numbers of symptoms within a cluster varied over time, whereas the specific symptoms within SCs were relatively stable.

Previous studies found similar SCs to ours by using multiple symptoms dimensions in oncology patients undergoing chemotherapy. For example, Sullivan et al.[9] identify four similar SCs to ours, including psychological, gastrointestinal, nutritional, and chemotherapy neuropathy, in breast cancer patients by using occurrence ratings and severity ratings. Three similar SCs (i.e., sickness behavior, nutritional, and psychological) were identified in lung cancer patients using the same dimensions in the results of Wong et al.[8] In addition, Suwisith et al.[11] identified three similar SCs (i.e., emotions-related, gastrointestinal, and image-related) based on severity ratings and distress ratings in breast cancer patients. We hypothesize that these results may lay a foundation for the future research in SC management and the pathophysiological mechanisms of SCs.

However, except for the sickness behavior at T2 and the body image at T1 and T3, the numbers of symptoms within the same type of SC varied among the three dimensions over time. This finding is dissimilar to the finding of Sullivan et al.[12] that five of eight SCs

*Table 2*
**Ratings of Symptom Occurrence, Severity, and Distress in Newly Diagnosed AML Patients at T1, T2, and T3 ($N = 126$)**

| | Occurrence Ratings % ($n$) | | | Severity Ratings Mean (SD) | | | Distress Ratings Mean (SD) | | |
|---|---|---|---|---|---|---|---|---|---|
| Symptoms | T1 | T2 | T3 | T1 | T2 | T3 | T1 | T2 | T3 |
| Difficulty concentrating | **51 (40.5)** | **87 (69.0)** | **86 (68.3)** | 0.69 (0.95) | 1.32 (1.11) | 1.24 (1.09) | 0.74 (1.13) | 1.39 (1.34) | 1.30 (1.36) |
| Pain | **60 (47.6)** | **69 (54.8)** | **62 (49.2)** | 0.98 (1.16) | 1.16 (1.20) | 0.98 (1.15) | 1.25 (1.44) | 1.44 (1.52) | 1.28 (1.56) |
| Lack of energy | 109 (86.5) | 111 (88.1) | 117 (92.9) | 1.75 (0.96) | 1.92 (1.06) | 2.02 (0.91) | 1.99 (1.21) | 2.19 (1.40) | 2.33 (1.21) |
| Cough | **34 (27.0)** | **39 (31.0)** | **44 (34.9)** | 0.55 (0.96) | 0.52 (0.86) | 0.69 (1.07) | 0.72 (1.28) | 0.64 (1.14) | 0.83 (1.36) |
| Feeling nervous | 102 (81.0) | **100 (79.4)** | **77 (61.1)** | 1.41 (0.88) | 1.32 (0.91) | 1.10 (1.05) | 1.49 (1.09) | 1.21 (1.08) | 0.99 (1.14) |
| Dry mouth | **42 (33.3)** | 108 (85.7) | **86 (68.3)** | 0.58 (0.91) | 1.91 (1.15) | 1.22 (1.07) | 0.46 (0.94) | 1.89 (1.39) | 1.13 (1.22) |
| Nausea | 16 (12.7) | **89 (70.6)** | **71 (56.3)** | 0.22 (0.62) | 1.56 (1.18) | 1.00 (1.02) | 0.22 (0.70) | 1.97 (1.52) | 1.20 (1.35) |
| Feeling drowsy | **41 (32.5)** | **90 (71.4)** | **99 (78.6)** | 0.54 (0.90) | 1.40 (1.04) | 1.44 (1.00) | 0.52 (0.98) | 1.18 (1.13) | 1.28 (1.10) |
| Numbness/tingling in hands/feet | 10 (7.9) | 20 (15.9) | 20 (15.9) | 0.16 (0.57) | 0.29 (0.73) | 0.29 (0.78) | 0.16 (0.63) | 0.36 (0.91) | 0.33 (0.92) |
| Difficulty sleeping | **66 (52.4)** | **85 (67.5)** | **73 (57.9)** | 0.94 (1.08) | 1.41 (1.18) | 1.16 (1.18) | 1.06 (1.27) | 1.64 (1.43) | 1.25 (1.34) |
| Feeling bloated | 13 (10.3) | **30 (31.0)** | **28 (22.2)** | 0.24 (0.78) | 0.65 (1.06) | 0.44 (0.92) | 0.25 (0.81) | 0.71 (1.21) | 0.50 (1.06) |
| Problems with urination | 4 (3.2) | 5 (4.0) | 4 (3.2) | 0.06 (0.32) | 0.04 (0.20) | 0.06 (0.34) | 0.04 (0.23) | 0.03 (0.17) | 0.04 (0.32) |
| Vomiting | 13 (10.3) | **82 (65.1)** | **62 (49.2)** | 0.15 (0.49) | 1.35 (1.13) | 0.87 (1.00) | 0.18 (0.64) | 1.66 (1.44) | 1.07 (1.28) |
| Shortness of breath | **61 (48.4)** | **65 (51.6)** | **68 (54.0)** | 0.92 (1.06) | 0.96 (1.11) | 0.83 (0.94) | 1.00 (1.23) | 0.96 (1.20) | 0.91 (1.15) |
| Diarrhea | 9 (7.1) | 21 (16.7) | **33 (26.2)** | 0.10 (0.42) | 0.37 (0.93) | 0.57 (1.06) | 0.11 (0.46) | 0.39 (1.04) | 0.64 (1.23) |
| Feeling sad | **75 (59.5)** | **82 (65.1)** | **80 (47.6)** | 0.95 (0.95) | 1.09 (0.97) | 1.02 (0.91) | 0.88 (1.00) | 1.02 (1.35) | 1.04 (1.05) |
| Sweats | **66 (52.4)** | **85 (67.5)** | **94 (74.6)** | 0.98 (1.08) | 1.48 (1.27) | 1.54 (1.18) | 0.92 (1.24) | 1.57 (1.45) | 1.60 (1.38) |
| Worrying | 121 (96.0) | 118 (93.7) | 119 (94.4) | 1.77 (0.71) | 1.56 (0.76) | 1.52 (0.75) | 1.79 (0.98) | 1.51 (1.02) | 1.46 (1.08) |
| Problems with sexual interest or activity | 14 (11.1) | 16 (12.7) | 16 (12.7) | 0.24 (1.00) | 0.22 (0.66) | 0.26 (0.76) | 0.16 (0.61) | 0.19 (0.68) | 0.24 (0.78) |
| Itching | 8 (6.3) | 13 (10.3) | **27 (21.4)** | 0.11 (0.48) | 0.22 (0.69) | 0.41 (0.89) | 0.11 (0.60) | 0.27 (0.82) | 0.43 (1.04) |
| Lack of appetite | **58 (46)** | 105 (83.3) | 104 (82.5) | 0.84 (1.06) | 1.87 (1.17) | 1.59 (1.06) | 0.90 (1.24) | 2.14 (1.49) | 1.69 (1.30) |
| Dizziness | **66 (52.4)** | **61 (48.4)** | **62 (49.2)** | 1.02 (1.13) | 0.87 (1.06) | 0.92 (1.08) | 1.14 (1.39) | 1.02 (1.27) | 1.09 (1.29) |
| Difficulty swallowing | 7 (5.6) | 12 (9.5) | 13 (10.3) | 0.10 (0.47) | 0.16 (0.54) | 0.16 (0.53) | 0.11 (0.52) | 0.20 (0.67) | 0.19 (0.72) |
| Feeling irritable | **47 (37.3)** | **60 (47.6)** | **24 (46.0)** | 0.60 (0.89) | 0.70 (0.82) | 0.79 (0.97) | 0.60 (0.93) | 0.71 (0.96) | 0.85 (1.07) |
| Mouth scores | 11 (8.7) | 18 (14.3) | **27 (21.4)** | 0.20 (0.68) | 0.25 (0.68) | 0.43 (0.93) | 0.23 (0.81) | 0.37 (0.95) | 0.51 (1.12) |
| Change in the way food tastes | **36 (28.6)** | **91 (72.2)** | **91 (72.2)** | 0.48 (0.86) | 1.60 (1.21) | 1.24 (1.02) | 0.55 (1.05) | 1.86 (1.48) | 1.48 (1.32) |
| Weight loss | 29 (17.3) | **56 (44.4)** | **58 (46.0)** | 0.37 (0.78) | 0.59 (0.75) | 0.69 (0.89) | 0.34 (0.79) | 0.60 (0.93) | 0.75 (1.03) |
| Hair loss | 6 (3.6) | 25 (19.8) | **68 (54.0)** | 0.07 (0.36) | 0.22 (0.47) | 0.87 (0.99) | 0.06 (0.33) | 0.29 (0.71) | 0.97 (1.21) |
| Constipation | 10 (8.0) | **44 (34.9)** | **32 (25.4)** | 0.14 (0.54) | 0.60 (0.92) | 0.37 (0.75) | 0.15 (0.61) | 0.70 (1.19) | 0.44 (0.92) |
| Swelling of arms or legs | 4 (3.2) | 9 (7.1) | 12 (9.5) | 0.08 (0.45) | 0.15 (0.58) | 0.12 (0.39) | 0.10 (0.54) | 0.20 (0.76) | 0.17 (0.59) |
| "I don't like myself" | 4 (3.2) | **28 (22.2)** | **41 (32.5)** | 0.05 (0.28) | 0.24 (0.46) | 0.48 (0.79) | 0.05 (0.28) | 0.25 (0.54) | 0.50 (0.85) |
| Changes in skin | **31 (24.6)** | **39 (31.0)** | **57 (45.2)** | 0.55 (1.03) | 0.60 (0.98) | 0.83 (1.09) | 0.61 (1.20) | 0.65 (1.15) | 0.87 (1.21) |

AML = acute myeloid leukemia; T1 = −6 to 0 days before chemotherapy; T2 = +1 to +7 days during chemotherapy; T3 = +1 to +7 days after chemotherapy; SD = standard deviation.
The data in bold are occurrence ratings of symptoms that appeared in > 20% and < 80% of patients.

*Table 3*

**SCs Identification and Comparison of Symptoms Within Each Cluster by Ratings of Occurrence, Severity, and Distress at T1, T2, and T3**

| | | T1 | | | T2 | | | T3 | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Symptom Clusters (SC) | Symptom | Occurrence | Severity | Distress | Occurrence | Severity | Distress | Occurrence | Severity | Distress |
| Nutritional | Cough | 0.522 | 0.457 | 0.532 | – | – | – | – | – | – |
| | Dry mouth | 0.584 | 0.512 | 0.551 | – | – | – | 0.433 | 0.407 | 0.443 |
| | Sweats | 0.549 | 0.618 | 0.420 | – | – | – | – | – | – |
| | Lack of appetite | 0.573 | – | – | – | – | – | – | – | – |
| | Change in the way food tastes | 0.605 | – | – | – | – | – | – | 0.409 | 0.479 |
| | Difficulty concentrating | – | – | – | – | – | – | – | – | 0.417 |
| | Mouth scores | – | – | – | – | – | – | 0.410 | 0.455 | – |
| | Weight loss | – | – | – | – | – | – | – | 0.466 | – |
| | Constipation | – | – | – | – | – | – | 0.459 | 0.536 | 0.485 |
| | "I don't like myself" | – | – | – | – | – | – | – | 0.517 | 0.427 |
| | Total symptoms in each SC / total symptoms in all SCs at one time point | 5/5 | 3/5 | 3/5 | 0 | 0 | 0 | 3/7 | 6/7 | 5/7 |
| | Percent agreement (%) | 100.0 | 60.0 | 60.0 | 0 | 0 | 0 | 42.9 | 85.7 | 71.4 |
| Sickness behavior | Difficulty sleeping | 0.442 | 0.416 | – | – | – | – | – | – | – |
| | Shortness of breath | 0.535 | 0.551 | 0.441 | – | – | – | – | – | – |
| | Feeling sad | 0.567 | 0.488 | 0.547 | – | – | – | – | – | – |
| | Dizziness | 0.411 | – | – | – | – | – | – | – | – |
| | Changes in skin | 0.493 | – | 0.456 | – | – | – | – | – | – |
| | Difficulty concentrating | – | – | – | – | 0.573 | 0.523 | – | – | – |
| | Change in the way food tastes | – | – | – | – | 0.465 | 0.507 | – | – | – |
| | "I don't look myself" | – | – | – | – | 0.438 | 0.403 | – | – | – |
| | Total symptoms in each SC / total symptoms in all SCs | 5/5 | 3/5 | 3/5 | 0 | 3/3 | 3/3 | 0 | 0 | 0 |
| | Percent agreement (%) | 100 | 60.0 | 60.0 | 0 | 100 | 100 | 0 | 0 | 0 |
| Neuropathy | Difficulty concentrating | 0.634 | 0.868 | 0.690 | – | – | – | – | – | – |
| | Feeling drowsy | 0.454 | 0.414 | 0.592 | – | – | – | – | – | – |
| | Feeling irritable | – | – | 0.479 | – | – | – | – | – | – |
| | Total symptoms in each SC / total symptoms in all SCs at one time point | 2/3 | 2/3 | 3/3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Percent agreement (%) | 66.7 | 66.7 | 100 | 0 | 0 | 0 | 0 | 0 | 0 |
| Gastrointestinal | Difficulty concentrating | – | – | – | 0.451 | 0.478 | 0.524 | 0.464 | 0.524 | 0.467 |
| | Nausea | – | – | – | 0.790 | 0.989 | 0.924 | 0.802 | 0.805 | 0.854 |
| | Vomiting | – | – | – | 0.904 | 0.814 | 0.882 | 0.769 | 0.876 | 0.850 |
| | Change in the way food tastes | – | – | – | – | 0.402 | 0.423 | – | – | – |
| | Feeling drowsy | – | – | – | – | – | – | 0.413 | 0.461 | – |
| | Sweats | – | – | – | – | – | – | – | – | 0.420 |
| | "I don't like myself" | – | – | – | – | – | – | 0.439 | – | – |
| | Total symptoms in each SC / total symptoms in all SCs at one time point | 0 | 0 | 0 | 3/4 | 4/4 | 4/4 | 5/6 | 4/6 | 4/6 |
| | Percent agreement (%) | 0 | 0 | 0 | 75.0 | 100 | 100 | 83.3 | 66.7 | 66.7 |

(*Continued*)

*Table 3*
**Continued**

| Symptom Clusters (SC) | Symptom | T1 | | | T2 | | | T3 | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Occurrence | Severity | Distress | Occurrence | Severity | Distress | Occurrence | Severity | Distress |
| Psychological | Feeling nervous | – | – | – | 0.435 | 0.747 | 0.696 | 0.551 | 0.747 | 0.686 |
| | Difficulty sleeping | – | – | – | 0.422 | 0.411 | – | – | 0.414 | – |
| | Shortness of breath | – | – | – | 0.439 | – | – | – | – | – |
| | Feeling sad | – | – | – | 0.589 | 0.750 | 0.542 | 0.534 | 0.684 | 0.839 |
| | Feeling irritable | – | – | – | – | – | – | – | 0.422 | – |
| | Total symptoms in each SC / total symptoms in all SCs at one time point | 0 | 0 | 0 | 4/4 | 3/4 | 2/4 | 2/4 | 4/4 | 2/4 |
| | Percent agreement (%) | 0 | 0 | 0 | 100 | 75.0 | 50.0 | 50.0 | 100 | 50.0 |
| Body image | Itching | – | 0.712 | 0.961 | – | – | – | 0.738 | 0.770 | 0.754 |
| | Changes in skin | – | – | – | – | – | – | 0.595 | 0.782 | 0.871 |
| | Mouth scores | – | 0.851 | 0.651 | – | – | – | – | – | – |
| | Total symptoms in each SC / total symptoms in all SCs at one time point | 0 | 2/2 | 2/2 | 0 | 0 | 0 | 2/2 | 2/2 | 2/2 |
| | Percent agreement (%) | 0 | 100 | 100 | 0 | 0 | 0 | 100 | 100 | 100 |
| Total variance explained (%) | | 32.64 | 37.85 | 34.62 | 19.80 | 27.06 | 25.90 | 25.16 | 32.92 | 32.50 |

SC = symptom cluster; T1 = −6 to 0 days before chemotherapy; T2 = +1 to +7 days during chemotherapy; T3 = +1 to +7 days after chemotherapy; – = factor loading<0.4.

identified using occurrence and severity ratings maintained the same number of symptoms in breast cancer patients undergoing chemotherapy over time. For example, the SCs of psychological, hormonal, and epithelial had the same number of symptoms at T1 (before chemotherapy) and T3 (two weeks after chemotherapy), whereas nutritional and gastrointestinal each had the same number at T3 and T2 (one week after chemotherapy), respectively. Furthermore, the percentage agreement of SCs also varied across the three dimensions in our study. This result is also dissimilar to the findings of Sullivan et al.[12] One possible explanation for these differences were that symptom occurrence and severity may assess more related dimensions of the symptom experience, while severity and distress may assess distinct dimensions.[27]

Nevertheless, in our study, some specific symptoms were consistently identified within the same SC over time. These included dry mouth, itching, difficulty concentrating, nausea, feeling nervous, and feeling sad. This result is partly supported by the prior studies. For example, Sullivan et al.[12] identified feeling nervous and feeling sad in the psychological SC and nausea in the nutritional SC in breast cancer using occurrence ratings and severity ratings. In addition, using the same dimensions in lung cancer patients, Wong et al. showed that difficulty concentrating, nausea, and vomiting were included in the sickness behavior SC while feeling nervous and feeling sad were consistently identified in the psychological SC in lung cancer.[8] These results suggested that the SCs might have shared a common mechanism or etiology (e.g., inflammation).[28]

None of the SCs identified using the multiple dimensions were consistently presented across all three time points of induction chemotherapy. This outcome conflicts with that of Sullivan et al.,[12] who found that the SCs of psychological, hormonal, gastrointestinal, and epithelial were consistently identified over time in breast cancer patients undergoing chemotherapy. These rather contradictory results may be because the evaluation time points (i.e., −6 to 0 days before chemotherapy, +1 to +7 days during chemotherapy, and +1 to +7 days after chemotherapy vs before chemotherapy, one week after chemotherapy, and two weeks after chemotherapy) have affected the SCs identification in oncology patients. However, five SCs were consistently identified at two time points in our study, such as nutritional, body image, sickness behavior, gastrointestinal, and psychological. A possible explanation for the consistency between two time points in our study is that some significant interindividual variation might have affected the patients' experiences of symptoms and SC identification, such as variation in patient situations (i.e., psychological and physical function), comorbidities, chemotherapy agents, and chemotherapy dose.

Finally, in our study, the factor solutions (i.e., clusters) that accounted for highest total variance in all symptoms were those based on the severity ratings over time. The total variance explained is used to explain the variability in the original variables. Normally, the higher the total variance explained is, the lower the data complexity and the less of loss of information in the model.[29] Thus, we suggested that the factor solution derived using the severity ratings fit the data better than did those derived using the occurrence ratings and distress ratings in AML patients undergoing induction therapy. This result is similar to the finding of Kim et al.,[10] which indicated that the severity ratings fit the data better than did occurrence ratings. By contrast, Sullivan et al.[12] found that both the numbers and types of SCs using ratings of occurrence and severity were similar in breast cancer patients over time ($n = 540$). In addition, Suwisith et al.[11] found that both the numbers and types of SCs were similar using the ratings of severity and distress in a cross-sectional study of 320 breast cancer patients. Our study results confirm the use of severity dimension for evaluating the trajectory of SCs in oncology patients following the treatment cycle.

### *Limitations*

There are several limitations to this study. This study identified symptoms at three time points after patients' induction therapy and, thus, may not be fully representative of the symptom experiences of AML patients' symptom experience, as the patients' symptom experience may change following the progress of the disease or treatment. In addition, symptoms with occurrence rates ≤20% and ≥80% were excluded from the EFA. Thus, their contributions to SC identification were not considered.

## *Conclusions*

The study concluded that the numbers of SCs identified using rating of occurrence, severity, and distress varied in AML patients undergoing induction therapy, through which the specific symptoms in individual SCs were relatively stable. In addition, the SCs derived using the severity ratings fit the data better than did those based on the occurrence ratings and distress ratings.

Our findings suggested that future research should continuously focus on evaluating the trajectory of SCs in AML patients undergoing chemotherapy cycle. Furthermore, the common mechanisms and etiologies of SCs should be important future areas of research.

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