Validating a Patient-Reported Outcomes–Derived Algorithm for Classifying Symptom Complexity Levels Among Patients With Cancer

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ABSTRACT

Background: The patient-reported outcomes (PROs) symptom complexity algorithm, derived from self-reported symptom scores using the Edmonton Symptom Assessment System and concerns indicated on the Canadian Problem Checklist, has not been validated extensively. **Methods:** This is a retrospective chart review study using data from the Alberta Cancer Registry and electronic medical records from Alberta Health Services. The sample includes patients with cancer who visited a cancer facility in Alberta, Canada, from February 2016 through November 2017 (n=1,466). **Results:** The effect size ($d=1.2$) indicates that the magnitude of difference in health status between the severe- and low-complexity groups is large. The symptom complexity algorithm effectively classified subgroups of patients with cancer with distinct health status. Using Karnofsky performance status, the algorithm shows a sensitivity of 70.3%, specificity of 84.1%, positive predictive value of 79.1%, negative predictive value of 76.7%, and accuracy of 77.7%. An area under the receiver operating characteristic of 0.824 was found for the complexity algorithm, which is generally regarded as good. This same finding was also regarded as superior to the alternative algorithm generated by 2-step cluster analysis (area under the curve, 0.721). **Conclusions:** The validity of the PRO-derived symptom complexity algorithm is established in this study. The algorithm demonstrated satisfactory accuracy against a clinician-driven complexity assessment and a strong correlation with the known group analysis. Furthermore, the algorithm showed a higher screening capacity compared with the algorithm generated from 2-step cluster analysis, reinforcing the importance of contextualization when classifying patients' symptoms, rather than purely relying on statistical outcomes. The algorithm carries importance in clinical settings, acting as a symptom complexity flag, helping healthcare teams identify which patients may need more timely, targeted, and individualized patient symptom management.

J Natl Compr Canc Netw 2020;18(11):1518–1525
doi: 10.6004/jnccn.2020.7586

Background

For patients with cancer, experiencing multiple concurrent symptoms is common.^{1–4} This concept has been described in a variety of ways, such as symptom clusters, symptom burden, or complex symptoms. Although these terms have similar meanings, the term “symptom complexity” is used in this article to capture the continuum of symptom experiences from mild/no symptoms to numerous concurrent severe symptoms. Patients who experience higher levels of symptom complexity tend to experience lower functioning and quality of life.^{2,5,6} Therefore, it is critical to identify patients experiencing severe symptom complexity so that timely, targeted symptom management can be delivered.

With research showing benefits of gathering outcome data directly from patients, it has become more common for standardized, validated questionnaires to be integrated into routine clinical practice.⁷ In 2012, Alberta Health Services (AHS) Cancer Care Alberta (CCA) began implementing the routine use of a standardized patient symptom questionnaire called “Putting Patients First” (PPF) at all 17 cancer facilities in order to raise clinician awareness of patients' concerns and symptoms. The PPF includes 2 standardized measures: the Revised Edmonton Symptom Assessment System (ESAS-r)^{8,9} and the Canadian Problem Checklist (CPC),¹⁰ selected in alignment with the national reporting criteria established by the Canadian Partnership Against Cancer (CPAC).¹¹

In the process of integrating these patient-reported outcomes (PROs) into routine clinical practice, we encountered several barriers, such as a perceived lack of time to address symptoms/concerns and issues with the interpretation of PROs. Although clinicians appreciated the ability to see PROs for each patient, they reported feeling overwhelmed by the number of PRO data points to assimilate into their clinical assessment. This feedback aligned with published research on barriers to using PROs in routine clinical practice that include interpretation and application issues.⁷ As a result, in 2017 a group of

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epidemiologists, statisticians, and clinicians gathered to develop a pragmatic PRO-driven symptom complexity algorithm based on the existing data already being collected in the Alberta practice environment. The intention was to design visual flags to overcome the clinical challenge of identifying which patients are experiencing numerous concurrent severe symptoms. Three visual flags (green, yellow, red) were developed to signify different categories of symptom complexity that could be reported by a patient at an encounter. Based on symptom complexity level, clinicians can easily access the full view of each individual's trended PRO symptoms to tailor their clinical response further as needed. The development process included a variety of actual patient symptom scenarios and case reviews with clinical teams to assess the fit of the complexity score with clinical reality, leading to further refinement of the algorithm.

As interest in using the symptom complexity level spread more broadly in the organization, a formal validation of the algorithm was required. This study was designed to validate the algorithm by (1) assessing the known-group validity, (2) calculating the accuracy indices for correctly identifying patients with cancer with different levels of symptom complexity, and (3) comparing the algorithm's overall screening capacity to an alternative algorithm, generated by 2-step cluster analysis.

Methods

Data Source

This is a retrospective study of symptom complexity in patients with cancer undergoing treatment in Alberta, Canada. This study uses the data from the Alberta Cancer Registry and the electronic medical records (EMRs) within CCA known as ARIA. This study did not require written consent from participants because this was part of a larger provincial quality improvement project to improve clinical capacity to identify, assess, and manage symptoms. Data were gathered during chart audits conducted to understand the magnitude of clinic redesign required to increase capacity for targeted symptom management.

This project complies with the Helsinki Declaration and the Alberta Research Ethics Community Consensus Initiative guidelines for quality improvement and evaluation. The ethical principles established by the Alberta Research Ethics Community Consensus Initiative screened this project and waived the need for full Research Ethics Board review. No harm was anticipated or reported in relation to this project.

Study Population

The research sample included a cohort of patients with advanced-stage cancer attending a palliative radiation

therapy clinic at a cancer facility in Alberta, Canada, from February 2016 through November 2017. Criteria for inclusion were (1) patients with cancer aged >18 years, (2) Alberta residents, and (3) PRO data from the ESAS-r, CPC, and EuroQol 5-level EQ-5D (EQ-5D-5L) in their EMR. A total of 1,466 patients with cancer were identified and 64 (4%) were excluded due to incomplete data, leaving a final study cohort of 1,402 patients.

Algorithms

The symptom complexity algorithm considers the unique combination of symptoms and concerns the patient has identified on their preclinic PPF questionnaire. It rates the self-reported severity of symptoms and the number of concerns indicated at a single visit and assigns a symptom complexity score (low/green, moderate/yellow, or severe/red) for the encounter (Figure 1). This summary score alerts the clinician to the level of symptom complexity the patient is experiencing so the clinical team can tailor their time allocation and care to best meet the patient's needs as displayed on their individual trended PRO graph. For this study, the moderate/yellow and low/green categories of symptom complexity were collapsed into a single category to facilitate comparison, even though it represents a potential loss of information. This combined group will be referred to as the "low-complexity group" in this article.

An alternative algorithm using a 2-step cluster analysis was used for the purposes of comparison. This alternate algorithm divides patients with cancer into groups with distinct levels of symptom severity (high vs low) by applying a 2-step cluster analysis to classify symptom

Figure 1. Symptom complexity algorithm.

Abbreviations: CPC, Canadian Problem Checklist; ESAS-r, Revised Edmonton Symptom Assessment System.

level, as proposed by Shi et al¹² in 2011. This type of exploratory analysis has been used to categorize homogenous groups when the grouping is not previously known.¹³

Measurements

The ESAS-r is a 10-item PRO measure of prevalent evidence-based symptoms experienced by patients with cancer. Each item is rated on a 0 to 10 scale of severity. The scale of “well-being” is not reported on because the scale caused confusion, in that some patients counted 0 as the worst possible score, whereas others counted 10 as the worst possible score. The “other” category was also not included because it could be used to report on a large variety of symptoms.

The CPC is an evidence-based, 54-item self-report checklist designed to identify common concerns that patients with cancer experience. It is used in conjunction with the ESAS-r and tracks concerns since the patient’s last visit.

The EQ-5D-5L is a standardized screening tool that measures health status and quality of life and is extensively validated in different studies.^{14,15} The EQ-5D-5L has 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. Patients make a selection to identify the best description of their current health status (Table 1). The EQ-5D-5L misery index score is an overall health status score, which combines the scores within all 5 dimensions. A score of 25 represents the poorest health status possible.¹⁶

Karnofsky performance status (KPS) is a validated tool widely used by oncology clinicians to assess the functional status of their patients.^{17,18} It allows for classification and stratification into 3 functional classifications based on KPS score ranges (100–80 = normal functional status; 70–50 = compromised functional status; and <50 = poor functional status).^{19,20} Previous studies have broadly used KPS as an outcome/standard in the validation of the ESAS.^{21–24} Furthermore, researchers have shown KPS, when combined with ESAS, to be useful for recoding symptom prevalence and intensity in patients with advanced cancer.²⁵ Consequently, KPS was used as a comparator for symptom complexity scores in this study. Table 2 lists the KPS definition rating (%) criteria.

Statistical Analysis

Different types of validity were assessed. We first evaluated the known-group validity by using the independent *t* test and the Cohen *d* effect size to compare the EQ-5D-5L misery index score between the severe- and low-complexity groups. The magnitude of effect size was based on the

Table 1. EuroQol 5-Level EQ-5D

Dimensions	Scorings
Mobility	
I have no problems walking about	1
I have slight problems walking about	2
I have moderate problems walking about	3
I have severe problems walking about	4
I am unable to walk about	5
Self-care	
I have no problems washing or dressing myself	1
I have slight problems washing or dressing myself	2
I have moderate problems washing or dressing myself	3
I have severe problems washing or dressing myself	4
I am unable to wash or dress myself	5
Usual activities (eg, work, study, housework, family, or leisure activities)	
I have no problems doing my usual activities	1
I have slight problems doing my usual activities	2
I have moderate problems doing my usual activities	3
I have severe problems doing my usual activities	4
I am unable to do my usual activities	5
Pain/Discomfort	
I have no pain or discomfort	1
I have slight pain or discomfort	2
I have moderate pain or discomfort	3
I have severe pain or discomfort	4
I have extreme pain or discomfort	5
Anxiety/Depression	
I am not anxious or depressed	1
I am slightly anxious or depressed	2
I am moderately anxious or depressed	3
I am severely anxious or depressed	4
I am extremely anxious or depressed	5

value of *d*, with 0.2 considered a small effect size, 0.5 considered a medium effect size, and 0.8 considered a large effect size.²⁶ Moreover, using KPS as a comparator, we computed the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for the symptom complexity algorithm by 2×2 frequency tables for a subset of the sample who also had a KPS completed at the same visit (*n* = 583). To determine whether the complexity algorithm performed consistently across demographic subgroups, we further stratified the population by sex and age groups and repeated the same analysis. Last, we compared the overall screening capacity

Table 2. Karnofsky Performance Status Rating (%) Criteria

100	Normal no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or to do active work
60	Requires occasional assistance but is able to care for most of his personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospital admission is indicated although death not imminent
20	Very sick; hospital admission necessary; active supportive treatment necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

of the 2 algorithms by using the area under the curve (AUC) of receiver operating characteristic (ROC). Data were exported into SPSS Statistics, version 25 (IBM Corp) for analysis and statistical significance was set a priori at $P < .05$.

Results

Sample Characteristics

Mean age at diagnosis was 63 years (SD, 13.3; range, 12–97; median, 63 years), and 50.3% were female. The most common tumor grouping was genitourinary (25.5%), followed by breast (22.8%), lung (19.5%), gastrointestinal (12.8%), hematologic (6.3%), gynecologic (5.8%), head and neck (2.1%), sarcoma (1.5%), unknown primary (1.4%),

endocrine (1.0%), cutaneous (0.9%), and central nervous system (0.6%).

Summary of Symptoms

The mean score on the ESAS-r as a whole was 2.78, demonstrating that patients generally score at the low end of the response range. The most outstanding symptom among this sample was tiredness (mean [M], 4.60; SD, 2.87; range, 0–10; interquartile range [IQR], 2.00–7.00), followed by pain (M, 3.61; SD, 3.02; range, 0–10; IQR, 1.00–6.00) and drowsiness (M, 3.14; SD, 2.93; range, 0–10; IQR, 0.00–5.00). The mildest symptom reported was nausea (M, 1.10; SD, 2.07; range, 0–10; IQR, 0.00–1.00). Figure 2 presents the distribution of symptom intensity based on the ESAS-r for this cohort by established cutoffs (0, 1–3, 4–6, and 7–10).

The CPC has 7 domains: emotional, social/family/spiritual, practical, physical, mobility, nutrition, and informational, and each domain has up to 15 more specific concerns. Of the total number of 54 specific concerns, the most frequently endorsed concern was walking/mobility ($n=559$), followed by fears/worries ($n=443$) and strength ($n=431$). The least endorsed concern was “How much alcohol you drink” ($n=11$). Table 3 lists the top 10 most endorsed concerns of this sample.

Prevalence of Symptom Complexity

For all 1,402 patients with cancer included in this study, a symptom complexity score was determined according to the proposed algorithm (Figure 1): severe ($n=543$; 38.7%; 99% CI, 35.4%–42.2%) and low ($n=859$; 61.3%; 99% CI, 57.8%–64.6%). Table 4 outlines the overall prevalence of symptom complexity levels by patient characteristics.

Figure 2. Distribution of symptom intensity based on the Revised Edmonton Symptom Assessment System.

Table 3. Top 10 Endorsed Concerns Based on the Canadian Problem Checklist

Concern	Domain	Number of Endorsement
Walking/Mobility	Mobility	559
Fears/Worries	Emotional	443
Strength	Physical	431
Sleep	Physical	370
Weight loss	Nutrition	365
Trouble with daily activities	Mobility	328
Frustration/Anger	Emotional	325
Sadness	Emotional	324
Worry about friends/family	Social/Family/Spiritual	321
Feeling like a burden to others	Social/Family/Spiritual	308

Table 4. Sample Characteristics by Patient Symptom Level

Characteristic	Symptom Complexity Level		P Value
	Low + Moderate	Severe	
Age, y			.125
<40	52	25	
40–49	71	41	
50–59	214	124	
60–69	269	156	
70–79	179	131	
≥80	74	66	
Sex			.186
Male	415	282	
Female	444	261	
Tumor group			.002
Genitourinary	197	161	
Breast	217	102	
Lung	155	118	
Gastrointestinal	110	69	
Hematologic	62	26	
Gynecologic	56	26	
Head & neck	14	14	
Sarcoma	15	6	
Unknown primary	8	11	
Endocrine	12	2	
Cutaneous	6	6	
Central nervous system	7	1	

Known-Group Validity

Known-group (discriminant) validity was assessed by determining whether the symptom complexity algorithm could differentiate among groups known to differ in health status. We compared health status between the 2 groups using the EQ-5D-5L misery index score as an indicator. The severe-complexity group reported significantly higher mean misery index scores than the low-complexity group (14.8 [95% CI, 14.4–15.1] vs 9.91 [95% CI, 9.64–10.2]; $P<.001$). A Cohen d of 1.2 indicated that the magnitude of difference in health status between the groups is large.

Accuracy Indices

Overall performance (sensitivity, specificity, PPV, NPV, and accuracy) was calculated using a subgroup of patients who also had a clinician-generated KPS score ($n=583$). This study chose a score $<50\%$ as the cutoff, which indicates the patient has low functionality and substantial care needs,^{27–29} and classified the patients into 2 groups—more complex (KPS score $<50\%$) versus less complex (KPS score $\geq 50\%$)—to correspond with the dichotomous classification by our complexity algorithm: severe symptoms versus low symptoms. Table 5 shows the validity indices obtained for the symptom complexity algorithm with 95% confidence intervals. We further stratified the cohort by sex and age and conducted the same calculations.

Comparison Between Algorithms

To make this comparison, we generated an alternative 2-step cluster analysis. With the 8 symptoms on ESAS-r as variables (“well-being” and “other” were excluded), the clustering solution was obtained using log-likelihood estimation, and the number of groups fixed ($n=2$). The 2-step cluster analysis generated a low-symptom group

($n=926$; 67.3%) and a severe-symptom group ($n=449$; 32.7%).

The ROC curve plots the probability of true-negative (specificity) versus the probability of false-positive (sensitivity) for various decision criteria, and therefore the larger the AUC, the more valid the diagnostic test is in comparison with the KPS comparator. The measure of the AUC will be between 0.5 for no detectability of the test (chance alone) and 1.0 for perfect detectability. An AUC >0.8 is generally considered adequate.³⁰ As presented in Figure 3A, the results revealed an AUC of 0.824 (95% CI, 0.790–0.858) for the symptom complexity algorithm, which confirmed its screening capacity and surpassed the AUC of 0.721 (95% CI, 0.679–0.762) for the 2-step cluster analysis algorithm (Figure 3B).

Discussion

Experiencing multiple concurrent symptoms has a profound impact on a patient's well-being, functional status, and quality of life. Unmanaged complex symptoms can

Table 5. Validity Indices

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)
Entire cohort	70.3% (64.4%–75.7%)	84.1% (79.6%–87.9%)	79.1% (74.3%–83.1%)	76.7% (73.2%–80.0%)	77.7% (74.1%–81.0%)
Sex					
Female	71.1% (62.1%–79.0%)	86.2% (79.8%–91.1%)	79.6% (72.3%–85.4%)	79.7% (74.6%–83.9%)	79.6% (74.4%–84.2%)
Male	69.6% (61.5%–76.9%)	81.9% (75.0%–87.7%)	78.6% (72.1%–84.0%)	73.8% (68.6%–78.5%)	75.9% (70.7%–80.6%)
Age group, y					
<40	60.0% (32.3%–83.7%)	100.0% (73.5%–100.0%)	100.0% (73.5%–100.0%)	66.7% (51.8%–78.8%)	77.8% (57.7%–91.4%)
40–49	81.8% (48.2%–97.7%)	76.0% (54.9%–90.6%)	60.0% (41.4%–76.1%)	90.5% (72.7%–97.1%)	77.8% (60.8%–89.9%)
50–59	66.0% (51.7%–78.5%)	93.9% (85.1%–97.8%)	87.5% (74.6%–94.4%)	79.6% (72.7%–85.1%)	82.0% (74.3%–88.3%)
60–69	74.7% (62.9%–84.2%)	89.4% (81.3%–94.8%)	84.1% (74.4%–90.6%)	82.4% (76.7%–87.5%)	83.0% (76.4%–88.4%)
70–79	65.8% (54.0%–76.3%)	72.0% (60.4%–81.8%)	70.4% (61.5%–78.0%)	67.5% (59.6%–74.5%)	68.9% (60.8%–76.2%)
≥80	85.0% (70.2%–94.3%)	67.6% (50.2%–82.0%)	73.9% (63.6%–82.1%)	80.7% (65.8%–90.0%)	76.6% (65.6%–85.5%)

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

also negatively impact adherence to recommended cancer treatments and clinical outcomes.³¹ Therefore, enhancing a clinician's ability to identify patients experiencing numerous concurrent severe symptoms increases the likelihood that targeted symptom management and supportive care will be provided within the clinical encounter.^{2–4} This algorithm is not meant to stand alone,

as the complexity level is a clinical flag for the healthcare team to review and address patients' individual reported symptoms and/or concerns. Nevertheless, this algorithm provides a simple, practical way to interpret and summarize a variety of PROs that aligns with recommendations that the interpretation of PROs should be simple and descriptive (eg, none, mild, moderate, severe).⁷

Figure 3. ROC curves: (A) complexity algorithm (AUC, 0.824), and (B) 2-step cluster algorithm (AUC, 0.721).

Abbreviations: AUC, area under the curve; ROC, receiver operating characteristic.

This validation study aimed to evaluate whether the PRO-derived symptom complexity algorithm could accurately and consistently identify patients with cancer experiencing distinct levels of complex symptoms. The reliability of this complexity score has immediate implications for clinical practice. At the micro level, in the clinical care process, patients with varying degrees of symptom complexity are easily identified in the preclinic phase so that the care team can make real-time decisions regarding which level of provider and which route of care (in-person vs virtual) is most suited for the level of symptom management the patient requires. At the meso level, administrators can adjust clinic templates and staffing levels in response to the distribution of symptom complexity among different clinical populations. At the macro level, program funding for symptom management and supportive care could be allocated to areas in which patient needs are prevalent. Based on these system-level impacts, the need for a robust validation study became apparent.

Known-group validity is a standard method of construct validation and is an important characteristic of a good PRO measure.³² Known-group analysis indicated the discriminant capacity of the PRO-derived symptom complexity algorithm for this population with cancer. Mean scores for the EQ-5D-5L misery index score were significantly higher for the severe-complexity subgroup, with a large effect size supporting that this algorithm effectively differentiated the severe-complexity subgroup from the low-complexity subgroup in regard to health status.

Using KPS as a clinical-derived comparator, the PRO-derived symptom complexity algorithm shows satisfactory sensitivity, specificity, predictive value, and accuracy for discriminating patients with severe symptom complexity from those with low symptom complexity. These results confirm the validity of the PRO-derived symptom complexity algorithm and is the basis for further validation work.

To make a comparison, we generated an alternative algorithm classification through 2-step cluster analysis.^{12,13} The AUC for our PRO-derived symptom complexity algorithm is greater than the alternative algorithm. This suggests the PRO-derived symptom complexity algorithm is superior to the alternative algorithm at detecting symptom complexity. This finding has an important implication: even though a statistical perspective is emphasized in many subject-matter areas, symptom complexity requires proper contextualization of the patient.³³

This study is not without limitations. The pragmatic design of our symptom complexity algorithm required retrospective validation, and therefore we had to select

from the available measures in our clinical EMR. We found KPS was the best possible assessment tool among available measures, because it has been widely used in ESAS validation studies.^{21–24} Further studies should be conducted with different reference standards and weighting of symptoms, and to measure the impact that changes to the algorithm would have on the algorithm's validity. Additionally, the study sample is composed of patients with advanced-stage cancer, which may impede generalizability.

Despite the limitations, this study has a few notable strengths, including sample size and lack of selection bias. The large number of participants in this study includes patients with cancer from both sexes, different ages, and different tumor groups, which increases the samples representativeness. Furthermore, these data were collected as part of routine clinical practice, rather than by research volunteers, which increases external validity.

We believe our study makes 2-fold contributions to current PRO-based research. It has validated an algorithm for ascertaining cases of high symptom complexity among patients with cancer based on their self-reported symptom burden, offering an alternative approach to identify individuals who require complex symptom management. Furthermore, even though PROs have been widely included in cancer research over the past decade, providers still express concerns about the reliability of patient outcomes and continue to show professional resistance to the engagement and empowerment of patients.^{34–36} This study confirms the concordance between PROs and clinical assessment and highlights the value of patients' input in describing their own symptoms.

Conclusions

This study demonstrated the validity of a PRO-derived algorithm designed to classify symptom complexity among patients with cancer with good discrimination and calibration. This algorithm is generalizable to similar cancer populations. As healthcare reform continues, use of a symptom complexity algorithm, in conjunction with patients' individual trended PROs, could help differentiate patient care needs based on their levels of symptom complexity. We propose this PRO-derived algorithm be adopted for future complexity-related studies, refinement, and enhancement.

Submitted August 13, 2019; accepted for publication May 7, 2020.

Author contributions: Study concept and design: Watson. Sample preparation: Photitai, Chmielewski, Smith. Critical feedback, research, and analysis: All authors. Manuscript preparation: Watson, Qi, Delure. Manuscript editing: Delure, Photitai.

Disclosures: The authors have disclosed that they have not received any financial consideration from any person or organization to support the preparation, analysis, results, or discussion of this article.

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