Identification of Patient-Reported Outcome Phenotypes Among Oncology Patients With Palliative Care Needs

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QUESTION ASKED: Can patient-reported outcome (PRO) data identify latent symptom phenotypes among oncology patients that characterize indications for specialty palliative care referral?

SUMMARY ANSWER: Self-reported symptoms from oncology patients referred to outpatient palliative care can be used to differentiate patients into clinically meaningful phenotypes that characterize multidimensional palliative needs.

WHAT WE DID: We applied latent profile analysis to self-reported symptoms on the Edmonton Symptom Assessment System collected from solid tumor oncology patients (N = 745) referred to outpatient palliative care. Data were collected as part of routine clinical care from October 2012 to March 2018 at eight community and academic sites. We applied latent profile analysis to identify PRO phenotypes and examined the association of phenotypes with clinical and demographic characteristics using multinomial logistic regression.

WHAT WE FOUND: We identified four latent PRO phenotypes among solid tumor oncology patients who were referred in real-world settings for palliative care evaluation (FIG 1). In a secondary analysis of 421 patients, we found that two brief questions assessing social and existential needs aligned with higher severity symptom and psychological distress phenotypes.

BIAS, CONFOUNDING FACTORS, DRAWBACKS: This analysis has limitations. First, the study is cross-sectional, which precludes our ability to validate the phenotypes based on response to palliative care intervention. Second, the sample consists of a large proportion of patients with lung cancer, which could bias the formation of latent subgroups. We conducted a sensitivity analysis restricted to patients with non–lung cancer, which resulted in little change to the model and suggested that influence was small. Third, the proportion of patients in the "Low" phenotype (39%) likely indicates undetected reasons for palliative care referral, such as advanced care planning needs or care coordination, that are not captured within the data set. Finally, since the PRO phenotypes are identified among oncology patients referred to palliative care, the phenotypes will likely identify the most high need patients in a general oncology population and will need further refinement to capture earlier palliative care needs.

REAL-LIFE IMPLICATIONS: The identified PRO phenotypes are clinically recognizable and potentially modifiable with clinical interventions and characterize appropriate and common indications for palliative care referral. Further research is needed to prospectively determine if PROs assessing multidimensional palliative domains of care can be used to identify patients for palliative care referral. As PRO monitoring grows in clinical practice and larger data sets are available for population-based research, latent modeling approaches may have increasing utility to identify distinct subgroups of patients to tailor supportive interventions.

ASSOCIATED CONTENT

Appendix

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abstract

PURPOSE Despite evidence-based guidelines recommending early palliative care, it remains unclear how to identify and refer oncology patients, particularly in settings with constrained access to palliative care. We hypothesize that patient-reported outcome (PRO) data can be used to characterize patients with palliative care needs. To determine if PRO data can identify latent phenotypes that characterize indications for specialty palliative care referral.

METHODS We conducted a retrospective study of self-reported symptoms on the Edmonton Symptom Assessment System collected from solid tumor oncology patients (n = 745) referred to outpatient palliative care. Data were collected as part of routine clinical care from October 2012 to March 2018 at eight community and academic sites. We applied latent profile analysis to identify PRO phenotypes and examined the association of phenotypes with clinical and demographic characteristics using multinomial logistic regression.

RESULTS We identified four PRO phenotypes: (1) Low Symptoms (n = 295, 39.6%), (2) Moderate Pain/Fatigue + Mood (n = 180, 24.2%), (3) Moderate Pain/Fatigue + Appetite + Dyspnea (n = 201, 27.0%), and (4) High Symptoms (n = 69, 9.3%). In a secondary analysis of 421 patients, we found that two brief items assessing social and existential needs aligned with higher severity symptom and psychological distress phenotypes.

CONCLUSION Oncology patients referred to outpatient palliative care in a real-world setting can be differentiated into clinically meaningful phenotypes using brief, routinely collected PRO measures. Latent modeling provides a mechanism to use patient-reported data on a population level to identify distinct subgroups of patients with unmet palliative needs.

INTRODUCTION

Early outpatient palliative care for patients with advanced solid tumors improves healthcare outcomes.[1-6] Several randomized trials have consistently shown significant improvements in quality of life, symptom burden, end-of-life care, and a potential survival benefit with the addition of early specialty palliative care to standard oncology treatment for patients with advanced cancer.[1-5,7] However, palliative care is not well-integrated into oncology practice despite clear recommendations for timely referral.[8,9] One major barrier to referral is the lack of clearly defined referral criteria for specialty palliative care, particularly in the setting of constrained access.[10-13] Current approaches for identifying patients with outpatient palliative care needs rely on disease characteristics, patient symptoms, clinician intuition, or measures of a patient's effect on health system costs, such as unplanned emergency room visits or hospital readmission.[14-17] Referral criteria would optimally consider direct patient report measured through standardized patient-reported outcomes (PROs), which may improve the identification of symptoms and timing of referral among oncology patients.

Symptom monitoring using PRO measures is uniquely suited to capture active, time-varying, and complex palliative needs directly from the patient. With the growing use of PRO symptom monitoring in oncology,[18-20] there is now an opportunity to study whether self-reported symptom data can direct the timing and appropriateness of palliative care referral. However, to use PRO data on a population level to

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identify patients' needs and direct care, we first need to develop computational methods to interpret large PRO data sets. Latent profile analysis (LPA) is a well-validated statistical approach that lends itself to interpretation of symptom data.[21-23]

LPA uses responses to survey questions to identify latent subgroups, with the hypothesis that patient membership in a subgroup may predict similar risk for future outcomes or differentiate response to interventions.[24] Although previous studies have examined symptom data to identify latent subgroups among oncology patients, these studies were not designed to identify subgroups of patients with actionable palliative care needs.[23,25,26] The application of these studies to inform development of PROs for palliative care referral is limited because of the use of heterogeneous patient populations and convenience sampling of PRO data. Thus, the primary aim of this study is to determine if PRO data can be used to identify latent phenotypes among oncology patients that characterize indications for palliative care referral. We then determine the association of latent phenotypes with demographic and clinical characteristics.

METHODS

Data Source and Population

We conducted a retrospective cross-sectional study of PROs reported by oncology patients at the time of their initial palliative care visit. Data were collected as part of routine clinical care from October 2012 to March 2018 at eight community and academic sites within the Global Palliative Care Quality Alliance (GPCQA).[27] To ensure high fidelity of data collection, we excluded sites with (1) 20% or greater missingness in any one of the nine PRO items included in the primary analysis and (2) low site volume, defined as $< 0.5\%$ of the total study population. The study population ($N = 894$) included all adult patients (≥ 18 years old) with a solid tumor diagnosis seen at an initial palliative care visit at one of the sites within the GPCQA, and 745 patients with complete PRO data were included in the primary analysis (Appendix Fig A1, online only, CONSORT diagram).

Data were collected using the Quality Data Collection Tool (QDACT), a secure Web-based interface used by clinicians to input data from patients at the point of care.[28] QDACT facilitates the structured assessment of palliative care domains and includes instruments that have been well-validated in oncology research and clinical practice. We selected the QDACT data set for several reasons: (1) a registry population representative of natural patterns of palliative care referral in the real-world setting from community and academic practices; (2) inclusion of PRO measures that assess multiple domains of palliative care, including physical, psychosocial, and existential distress; and (3) inclusion of disease-specific (tumor type and stage) and clinical (performance status and provider prognostic estimation) data elements. This study was approved by the Duke Institutional Review Board (Pro00035703).

Measures

PRO measures in the QDACT registry were selected through literature review and national quality guidelines for symptom assessment in palliative care.[28,29] Demographics and clinical data are collected at the beginning of the palliative care visit and include the following categories.

Sociodemographic variables. Sociodemographic variables are age at time of consultation, sex, race, and partner status.

Clinical variables. Clinical variables are tumor type, stage, referring specialty, palliative performance scale, and provider prognostic estimation.

Symptoms. Physical and psychological symptoms are assessed using the Edmonton Symptom Assessment System (ESAS), a widely used self-reporting tool of symptom intensity developed for the oncology patient population.[30] Symptoms are rated on a 0-10 numerical rating scale, in which 0 means that the symptom is not present and 10 means that the symptom is the "worst possible" and include pain, shortness of breath, constipation, fatigue, nausea, drowsiness, appetite, depression, anxiety, and well-being.

Palliative needs. Existential distress ("Are you at peace?") and social distress ("At times I worry I will be a burden to my family.") are each assessed with a single question that has been modified from existing instruments for feasibility of collection in routine clinical care.[28] These questions were developed by the QDACT investigators in collaboration with the GPCQA and by consultation with national experts and then refined through multiple iterations for clinical utility based on patient and provider feedback (Appendix Table A1, online only).

Statistical Analysis

Latent profile analysis. We hypothesized that particular combinations of responses to the ESAS symptom questions (indicator variables) would define clinically relevant PRO phenotypes (latent subgroups) that characterize indications for specialty palliative care referral. LPA uses finite mixture models to identify unobserved latent subgroups that are defined by a set of indicator variables.[24] Statistical analysis was conducted using Stata Version 15.1.

The ESAS "well-being" item was excluded because of potential measurement error that resulted from a reverse rating, that is, 0 is worst well-being and 10 is best well-being. We treated the answer option "patient unable to respond" as missing because it showed inconsistent patterns of response across symptoms for individual patients. We compared the ESAS complete case population ($n = 745$) with the population with missing ESAS data and found potential differences in performance status and provider-estimated prognosis (interpretation limited by

missingness), but otherwise no differences in demographic and clinical characteristics (Appendix Table A2). We then proceeded with a complete case analysis.

To determine the optimal number of latent subgroups, we used an exploratory approach and compared model fit indices for increasing numbers of classes until the Akaike information criterion and Bayesian information criterion plateaued, resulting in an analysis of 2-6 classes (Appendix Fig A2). To determine the final model, lower values of Akaike information criterion and Bayesian information criterion were considered in conjunction with clinical interpretability of the subgroups to reach an optimal balance between model fit and clinical relevance. We characterized the severity and types of ESAS symptoms to describe PRO phenotypes and then assigned latent subgroup membership to each patient in the data set based on the highest predicted probability of subgroup membership (posterior probability).

Patients' clinical and demographics characteristics were summarized as mean (standard deviation) for continuous variables and frequency (%) for categorical variables. Analysis of variance and chi-square test were used to compare continuous and categorical variables, respectively, across the PRO phenotypes. To determine construct validity of the PRO phenotypes, we evaluated whether demographics and clinical characteristics follow expected patterns across phenotypes. We hypothesized that selected characteristics (age, sex, race, relationship status, Palliative Performance Scale [PPS], provider prognostic estimation, cancer type, and stage) would associate with symptom phenotypes. We estimated these associations in a multiple multinomial logistic regression model, with the PRO phenotypes as the outcome and phenotype "Low Symptoms" as the reference group.

Social and existential distress measures. To explore how social and existential distress measures may inform phenotypes, we performed a secondary LPA that included two additional questions regarding these perceived states, respectively (ie, "worry about family burden" and being "not at peace"). Four hundred twenty-one patients with complete data for the additional measures contributed to this analysis. Likert scale responses were converted into binary variables (present or not present) to increase power (Appendix Table A1).

Sensitivity analysis. Given the high prevalence of lung cancer in the cohort, we performed a sensitivity analysis to assess whether phenotypes identified in the primary analysis were driven by the largest disease group. We excluded patients with lung cancer and examined whether the resulting phenotypes were similar to those of the full sample.

RESULTS

Table 1 shows clinical and demographic characteristics of the total study population (N = 745) and latent symptom phenotypes. Notably, 38.3% of patients have a PPS score of 40-60 (approximately Eastern Cooperative Oncology Group [ECOG] 2-3) and 46.3% have an estimated prognosis of < 6 months.

LPA: Identification of PRO Phenotypes

The LPA model includes nine symptom indicators: pain, shortness of breath, constipation, fatigue, nausea, drowsiness, appetite, depression, and anxiety. We identified four PRO phenotypes (Fig 1): (1) Low Symptoms ("Low", n = 295, 39.6%), (2) Moderate Pain/Fatigue + Mood ("Mood", n = 180, 24.2%), (3) Moderate Pain/Fatigue + Appetite + Dyspnea ("Moderate Physical", n = 201, 27.0%), and (4) High Symptoms ("High", n = 69, 9.3%). The four-class model achieves an optimal balance between model fit and parsimony of phenotypes for clinical application as a screening tool. Descriptively, patients in the "Low" and "High" phenotypes have nonoverlapping severity profiles. The two "Moderate" phenotypes are most clinically differentiated from each other by mood severity, in which patients in the "Mood" phenotype have higher reports of anxiety and depression.

Demographic and Clinical Associations With PRO Phenotypes

We examined associations between PRO phenotypes and patient demographic and clinical characteristics using the "Low" phenotype as the reference group (Table 2). We did not find significant differences in race, relationship status, or sex among patients by PRO phenotypes. However, conclusions regarding race and relationship status are limited by the small percentage of non-White patients in the study population and missing data in these variables. Point estimates of association with PRO phenotype and cancer type show a trend toward differences across symptom phenotypes but did not reach statistical significance. Age is significantly associated with phenotype membership. Patients of younger age (age, 25-55) are more likely to be associated with all symptomatic phenotypes and especially associate with the "Mood" phenotype compared with older patients (age, 25-55, odds ratio [OR], 5.16, 95% CI, [2.56 to 10.38]; age $>$ 55-74; OR, 2.58, 95% CI [1.43 to 4.66]). Regarding disease stage, patients with nonmetastatic disease are more likely to be in the "High" versus "Low" phenotype at the time of palliative evaluation compared with patients with metastatic disease ("High" OR, 2.82, 95% CI [1.27 to 6.26]).

Point estimates of PPS scores show an increasing graded response relationship with worsening severity of PRO phenotypes ("Mood" OR, 1.99; 95% CI [1.27 to 3.10]; "Moderate Physical" OR, 2.58; 95% CI [1.69 to 3.94]; and "High" OR; 3.76, 95% CI [2.05 to 6.90]). For example, patients with a PPS 40-60 (ie, ECOG 2-3) are approximately 3.8 times more likely to be associated with the "High" phenotype compared with patients with a PPS 70-100 (ie, ECOG 0-1).

TABLE 1. Clinical and Demographic Characteristics of Study Population Stratified by PRO Phenotypes

Characteristic	Total Population (N = 745)	PRO Phenotypes				P[a]
		Low Symptoms (n = 295; 39.6%)	Moderate Pain/Fatigue + Mood (n = 180, 24.2%)	Moderate Pain/Fatigue + Appetite + Dyspnea (n = 201; 27.0%)	High Symptoms (n = 69, 9.30%)	
Age						.006
> 74	148 (19.9%)	70 (23.7%)	24 (13.3%)	45 (22.4%)	14 (20.3%)	
> 55 to 74	306 (41.1%)	116 (39.3%)	85 (47.2%)	81 (40.3%)	23 (33.3%)	
25 to 55	158 (21.2%)	48 (16.3%)	54 (30.0%)	35 (17.4%)	17 (24.6%)	
Missing	133 (17.9%)	61 (20.7%)	17 (9.4%)	40 (19.9%)	15 (21.7%)	
Age, mean (SD)	64.1 (13.2)	65.9 (13.3)	61.1 (13.6)	65.4 (12.5)	61.9 (12.3)	.001
Sex						.023
Male	226 (30.3%)	90 (30.5%)	51 (28.3%)	67 (33.3%)	18 (26.1%)	
Female	385 (51.7%)	145 (49.2%)	111 (61.7%)	93 (46.3%)	36 (52.2%)	
Missing	134 (18.0%)	60 (20.3%)	18 (10.0%)	41 (20.4%)	15 (21.7%)	
Race						.19
White	521 (69.9%)	203 (68.8%)	135 (75.0%)	139 (69.2%)	44 (63.8%)	
Black	37 (5.0%)	13 (4.4%)	12 (6.7%)	9 (4.5%)	3 (4.3%)	
Others	12 (1.6%)	3 (1.0%)	5 (2.8%)	2 (1.0%)	2 (2.9%)	
Missing	175 (23.5%)	76 (25.8%)	28 (15.6%)	51 (25.4%)	20 (29.0%)	
Relationship status						.30
Married or partnered	337 (45.2%)	126 (42.7%)	95 (52.8%)	92 (45.8%)	24 (34.8%)	
Divorced or widowed	127 (17.0%)	55 (18.6%)	32 (17.8%)	31 (15.4%)	9 (13.0%)	
Single or never married	78 (10.5%)	31 (10.5%)	26 (14.4%)	12 (6.0%)	9 (13.0%)	
Missing	203 (27.2%)	83 (28.1%)	27 (15.0%)	66 (32.8%)	27 (39.1%)	
Referring specialty						.94
Oncology	677 (90.9%)	266 (90.2%)	165 (91.7%)	182 (90.5%)	64 (92.8%)	
General medicine	41 (5.5%)	18 (6.1%)	9 (5.0%)	10 (5.0%)	4 (5.8%)	
Others	25 (3.4%)	10 (3.4%)	5 (2.8%)	9 (4.5%)	1 (1.4%)	
Missing	2 (0.3%)	1 (0.3%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	
Palliative Performance Scale (PPS)[b]						< .001
PPS 70-100	446 (59.9%)	214 (72.5%)	106 (58.9%)	95 (47.3%)	31 (44.9%)	
PPS 40-60	285 (38.3%)	77 (26.1%)	70 (38.9%)	102 (50.7%)	36 (52.2%)	
Missing	14 (1.9%)	4 (1.4%)	4 (2.2%)	4 (2.0%)	2 (2.9%)	
Provider prognostic estimation						< .001
> 6 Months	336 (45.1%)	166 (56.3%)	87 (48.3%)	60 (29.9%)	23 (33.3%)	
< 6 Months	345 (46.3%)	107 (36.3%)	80 (44.4%)	121 (60.2%)	37 (53.6%)	
Missing	64 (8.6%)	22 (7.5%)	13 (7.2%)	20 (10.0%)	9 (13.0%)	
Cancer type						.004
Lung	211 (28.3%)	78 (26.4%)	44 (24.4%)	67 (33.3%)	22 (31.9%)	
Breast	81 (10.9%)	32 (10.8%)	26 (14.4%)	11 (5.5%)	12 (17.4%)	
Colorectal	49 (6.6%)	24 (8.1%)	11 (6.1%)	11 (5.5%)	3 (4.3%)	
Gynecologic	141 (18.9%)	51 (17.3%)	44 (24.4%)	33 (16.4%)	13 (18.8%)	
Pancreas	51 (6.8%)	17 (5.8%)	5 (2.8%)	22 (10.9%)	7 (10.1%)	
Upper GI and liver	57 (7.7%)	20 (6.8%)	17 (9.4%)	15 (7.5%)	5 (7.2%)	
Genitourinary	47 (6.3%)	20 (6.8%)	10 (5.6%)	17 (8.5%)	0 (0.0%)	

(continued on following page)

TABLE 1. Clinical and Demographic Characteristics of Study Population Stratified by PRO Phenotypes (continued)

Characteristic	Total Population (N = 745)	PRO Phenotypes				
		Low Symptoms (n = 295; 39.6%)	Moderate Pain/Fatigue + Mood (n = 180, 24.2%)	Moderate Pain/Fatigue + Appetite + Dyspnea (n = 201; 27.0%)	High Symptoms (n = 69, 9.30%)	*P*[a]
Others[c]	106 (14.2%)	52 (17.6%)	22 (12.2%)	25 (12.4%)	7 (10.1%)	
Missing	2 (0.3%)	1 (0.3%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	
Stage						.23
Metastatic	650 (87.2%)	258 (87.5%)	161 (89.4%)	176 (87.6%)	55 (79.7%)	
Nonmetastatic	95 (12.8%)	37 (12.5%)	19 (10.6%)	25 (12.4%)	14 (20.3%)	

Abbreviations: PRO, patient-reported outcome; SD, standard deviation.

[a]*P* value of a significance test is obtained across the PRO phenotypes using analysis of variance for continuous variables and chi-square test for categorical variables.

[b]PPS 70-100 approximately equivalent to Eastern Cooperative Oncology Group 0-1; PPS 40-60 approximately equivalent to Eastern Cooperative Oncology Group 2-3.

[c]Includes thyroid, head and neck, brain, and melanoma.

Social and Existential Distress Measures

In a secondary analysis using social and existential distress measures (n = 421), we identified a four-class solution with descriptively similar phenotypes (Fig 2). Social and existential distress needs group with phenotypes that have higher severity symptoms and psychological distress. The conditional probability of being "not at peace" is .86 in the "Mood" phenotype and .73 in the "High" phenotype (compared with .33 in "Low"). The conditional probability of "worry about family burden" is .88 in the "High" phenotype and .69 in the "Mood" phenotype (compared with .38 in "Low").

Sensitivity Analyses

In a sensitivity analysis to assess the effect of lung cancer prevalence on the formation of symptom phenotypes, removal of patients with lung cancer (n = 211, 28.3%) did not change the latent profile model or predicted probabilities of class membership (Fig A3).

DISCUSSION

We identified four latent PRO phenotypes among solid tumor oncology patients who were referred in real-world settings for palliative care evaluation (Fig 1). The PRO phenotypes have good construct validity, with factors known to be associated with higher patient distress such as younger age and worse functional status associated with more severe symptom phenotypes.[25,31,32] In a secondary analysis using two social and existential distress items, these domains grouped with symptom severity and psychological distress phenotypes. The identified PRO phenotypes are clinically recognizable (Fig 2) and potentially modifiable with clinical interventions and characterize appropriate and common indications for palliative care referral across physical, psychosocial, and existential domains. Collectively, these findings suggest that patient-reported symptoms could be used on a population level to identify patients with unmet palliative needs.

Current efforts to triage patients to specialty palliative care rely on demographic, disease, and prognostic factors. Our study examined the association of PRO phenotypes with these factors. Younger age is significantly associated with all symptomatic phenotypes and has the strongest association with the "Mood" phenotype. This finding is consistent with previous subgroup analyses of oncology patients, which found correlation of symptom occurrence with psychological distress and higher psychological distress among younger patients.[23,25] Importantly, current referral criteria consider those of older age, not younger age, as an indicator for palliative care. We also examined disease severity. Patients with nonmetastatic disease are more likely to be associated with the "High" phenotype compared with "Low," which we hypothesize reflects referral patterns. Patients with nonmetastatic disease may be referred for high symptom burden, whereas those with metastatic disease may be referred for other palliative needs such as advanced care planning or medical decision making that are not captured in this data set. Finally, there is a graded increase in association with performance status and higher severity symptoms. Taken together, these associations are clinically representative and overall provide good construct validity for the latent profile model.

In a secondary analysis using two additional questions to assess for social and existential distress, we identified a four-class model that is descriptively similar to the primary analysis with similar predicted proportions for each PRO phenotype (Fig 2). Patients are more likely to report "not being at peace" (existential distress) or "worry about being a burden to family" (social distress) in both the mood-

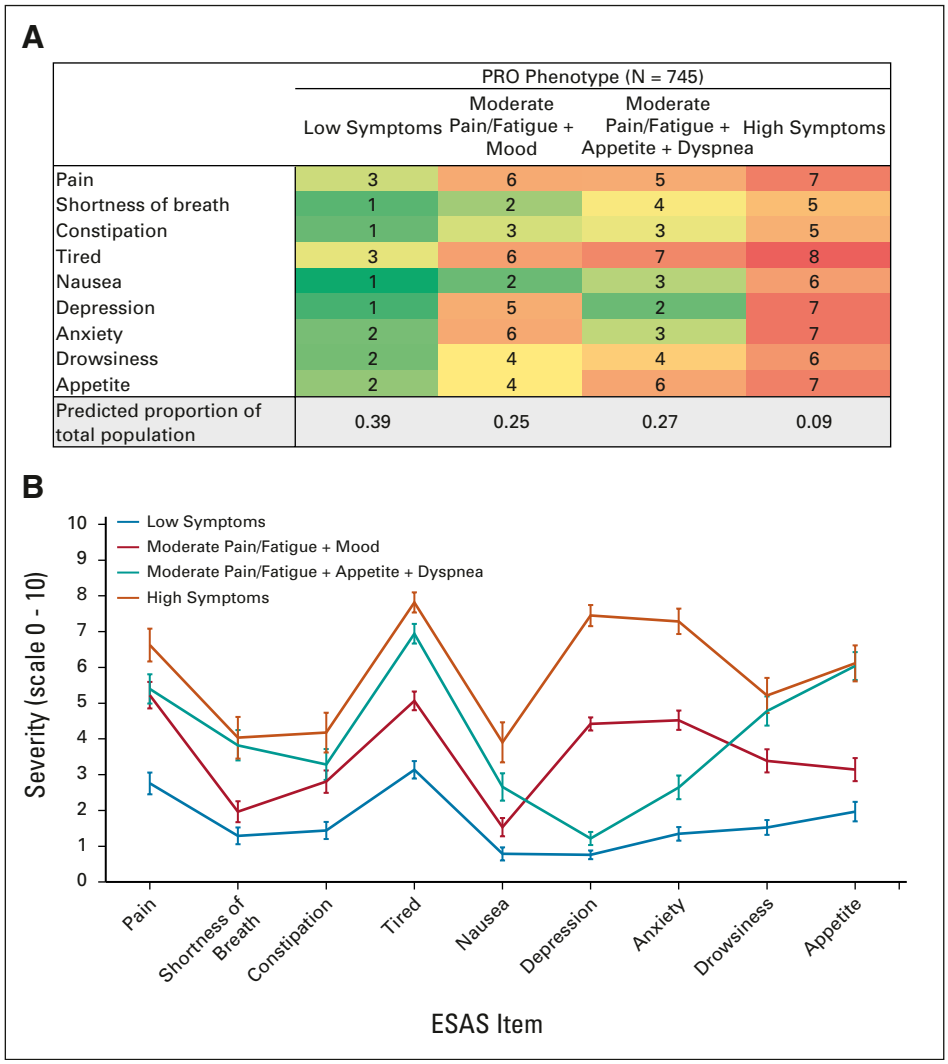

FIG 1. (A) Latent profile model: four-class solution. Depiction of the results of the latent profile model, which shows mean ESAS severity ratings (0-10) predicted by the model for each PRO phenotype. Symptom severity is represented by a graded color scale from green (low) to red (high). (B) Mean ESAS item severity ratings by PRO phenotype. Depiction of mean ESAS severity ratings with confidence intervals observed for patients within each PRO phenotype. Patients are assigned to a PRO phenotype based on the predicted probability of class membership from the latent profile model. Patients have different profiles of symptom type and severity based on PRO phenotype membership. ESAS, Edmonton Symptom Assessment System; PRO, patient-reported outcome.

predominant and high severity phenotypes. Furthermore, patients are most likely to report not being at peace in the "Mood" phenotype and most likely to report worry about burden on family in the "High" symptom phenotype. These groupings clinically make sense, as patients with high symptom burden likely require more caregiver support and patients with mood-predominant symptoms likely have more difficulty with coping. We hypothesize that the addition of existential and social domains to PRO-based screening for palliative needs may help tailor supportive services, such as targeting social work services to patients who report "worry about family burden." Further research is needed to prospectively determine if PROs assessing multidimensional palliative domains of care improve the utility of PROs to identify patients with unmet specialty referral needs.

Our findings are overall consistent with previous subgroup analyses of oncology patients, which have shown the formation of low, moderate, and high symptom groups with a mood-predominant phenotype.[23,25] No previous studies have examined latent modeling of PROs in a palliative care population. This analysis improves upon these studies and significantly advances the field toward clinical application in several ways. First, this study models symptom data using continuous severity scales rather than "present or not

TABLE 2. Association of Covariates With PRO Phenotypes

	PRO Phenotypes					
	Moderate Pain/Fatigue + Mood		Moderate Pain/Fatigue + Appetite + Dyspnea		High Symptoms	
Covariate	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Age						
> 74	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—
> 55-74	2.58 (1.43 to 4.66)	.002[a]	1.57 (0.93 to 2.66)	.09	1.31 (0.58 to 2.98)	.51
25-55	5.16 (2.56 to 10.38)	< .001[a]	2.39 (1.22 to 4.71)	.01[a]	2.98 (1.13 to 7.85)	.03[a]
Missing	2.53 (0.26 to 24.46)	.42	0.60 (0.07 to 5.35)	.65	1.19 (0.02 to 73.14)	.93
Sex						
Male	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—
Female	1.10 (0.64 to 1.89)	.72	0.99 (0.59 to 1.66)	.98	1.01 (0.46 to 2.24)	.98
Missing	0.85 (0.08 to 9.07)	.89	2.24 (0.23 to 21.52)	.49	0.59 (0.01 to 38.76)	.81
Race						
White	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—
Non-White	1.49 (0.69 to 3.21)	.31	1.06 (0.44 to 2.51)	.90	1.56 (0.51 to 4.8)	.44
Others	1.27 (0.54 to 3.02)	.59	0.87 (0.36 to 2.06)	.74	1.47 (0.47 to 4.6)	.51
Relationship status						
Married or partnered	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—
Divorced or widowed	0.74 (0.43 to 1.28)	.28	0.72 (0.41 to 1.26)	.25	0.55 (0.22 to 1.43)	.22
Single or never married	0.79 (0.41 to 1.52)	.48	0.46 (0.20 to 1.02)	.06	1.25 (0.47 to 3.29)	.65
Missing	0.39 (0.17 to 0.91)	.03[a]	1.16 (0.60 to 2.27)	.66	1.96 (0.8 to 4.79)	.14
Palliative Performance Scale (PPS)						
PPS 40-60	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—
PPS 40-60	1.99 (1.27 to 3.10)	.002[a]	2.58 (1.69 to 3.94)	< .001[a]	3.76 (2.05 to 6.9)	< .001[a]
Provider prognostic estimation						
> 6 months	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—
< 6 months	1.71 (1.09 to 2.67)	.02[a]	2.65 (1.70 to 4.13)	< .001	2.36 (1.21 to 4.62)	.01[a]
Missing	1.12 (0.46 to 2.72)	.80	2.41 (1.09 to 5.31)	.03	2.24 (0.81 to 6.24)	.12
Cancer type						
Lung	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—
Breast	1.42 (0.69 to 2.94)	.34	0.51 (0.22 to 1.16)	.11	1.73 (0.66 to 4.48)	.26
Colorectal	0.84 (0.35 to 2.00)	.70	0.48 (0.21 to 1.11)	.09	0.48 (0.12 to 1.83)	.28
Gynecologic	1.30 (0.69 to 2.46)	.42	0.91 (0.48 to 1.74)	.78	1.17 (0.46 to 2.98)	.74
Pancreas	0.68 (0.22 to 2.07)	.50	1.66 (0.76 to 3.62)	.21	1.65 (0.55 to 4.93)	.37
Upper GI and liver	1.65 (0.75 to 3.66)	.22	0.84 (0.38 to 1.87)	.67	0.86 (0.27 to 2.77)	.80
Genitourinary	1.01 (0.40 to 2.51)	.99	1.20 (0.53 to 2.70)	.67	No Event	
Others	0.82 (0.41 to 1.63)	.57	0.72 (0.38 to 1.36)	.31	0.52 (0.19 to 1.42)	.20
Stage						
Metastatic	1.00 (reference)	—	1.00 (reference)	—	1.00 (reference)	—
Nonmetastatic	1.36 (0.70 to 2.64)	.36	1.45 (0.78 to 2.68)	.24	2.82 (1.27 to 6.26)	.01[a]

NOTE. All variables are included in a multinomial logistic regression model, and ORs are adjusted. ORs are interpreted as odds of PRO phenotype membership in a level of a covariate compared with odds of Low Symptoms phenotype membership in the reference level of a covariate, adjusting for other covariates.

Abbreviations: OR, odds ratio; PRO, patient-reported outcome.

[a]$P < .05$.

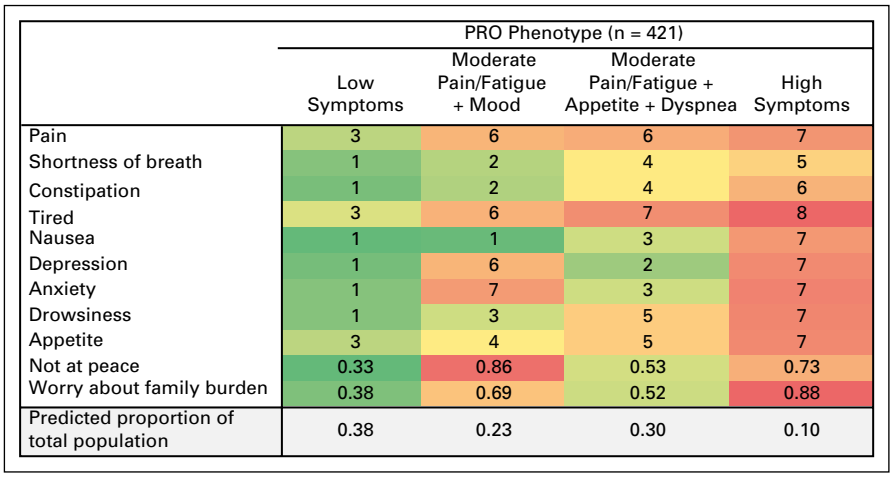

FIG 2. Latent profile model with existential and social distress measures. Depiction of symptom profiles for the four PRO phenotypes with two additional measures for being "not at peace" or having "worry about burden on family." Symptom severity is represented by a graded color scale from green (low) to red (high). For the ESAS items, a patient's severity rating (0-10) is predicted by the latent profile model based on membership in each PRO phenotype. For the "peace" and "burden" measures, the model reports the conditional probability of a patient screening positive for distress given membership in each PRO phenotype. ESAS, Edmonton Symptom Assessment System; PRO, patient-reported outcome.

present" cutoffs, which may increase the utility of PRO phenotypes as referral criteria by more accurately characterizing symptom burden. Second, the study design captures a snapshot of a referred patient population before palliative intervention. By defining a clinically relevant study population and time point for PRO collection, our findings can be applied in future validation studies. Third, no previous subgroup analyses have incorporated patient-reported measures of social and existential distress. Brief screening questions for these domains are associated with more severe phenotypes and may provide added utility for screening for palliative needs. Finally, the data set includes a comprehensive set of palliative domain measures collected at multiple clinical sites, which strengthens the validity and generalizability of our findings.

This analysis has limitations. First, the study is cross-sectional, which precludes our ability to validate the phenotypes based on response to palliative care intervention. However, we believe that the PRO phenotypes are clinically relevant given their good construct validity, coupled with the strong evidence base linking unmet symptom needs to adverse patient outcomes.[1,3,4,18-20] Second, the sample consists of a large proportion of patients with lung cancer, which could bias the formation of latent subgroups. To address this concern, we conducted a sensitivity analysis restricted to patients with non-lung cancer, which resulted in little change to the model and suggested that influence was small. Third, the proportion of patients in the "Low" phenotype (39%) likely indicates undetected reasons for palliative care referral, such as advanced care planning needs or care coordination, that are not captured within the data set. Fourth, we excluded patients with missing ESAS data, which could result in selection bias toward a healthier population. However, we believe that this bias is small given the large proportion of patients with poor prognosis and performance status included in the study population. Finally, although we did detect statistically significant associations of demographic and clinical characteristics with PRO phenotypes, the precision of these estimates is low because of stratification by latent subgroups. Given the above limitations, the identified PRO phenotypes should be refined and validated in a prospective study to develop PRO-based referral criteria for palliative care.

In summary, our findings suggest that a brief set of PRO measures collected in routine clinical practice can be used to identify PRO phenotypes that characterize physical, psychosocial, and existential distress needs. Future research is needed to validate PRO phenotypes in a patient population before referral. Since the PRO phenotypes are identified among oncology patients referred to palliative care, the phenotypes will likely identify the most high need patients in a general oncology population and will need further refinement to capture earlier palliative care needs. As PRO monitoring grows in clinical practice and larger data sets are available for population-based research,[33] latent modeling approaches may have increasing utility to guide supportive interventions to improve health outcomes.

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Data analysis and interpretation: All authors
Manuscript writing: All authors
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Identification of Patient-Reported Outcome Phenotypes Among Oncology Patients With Palliative Care Needs

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APPENDIX

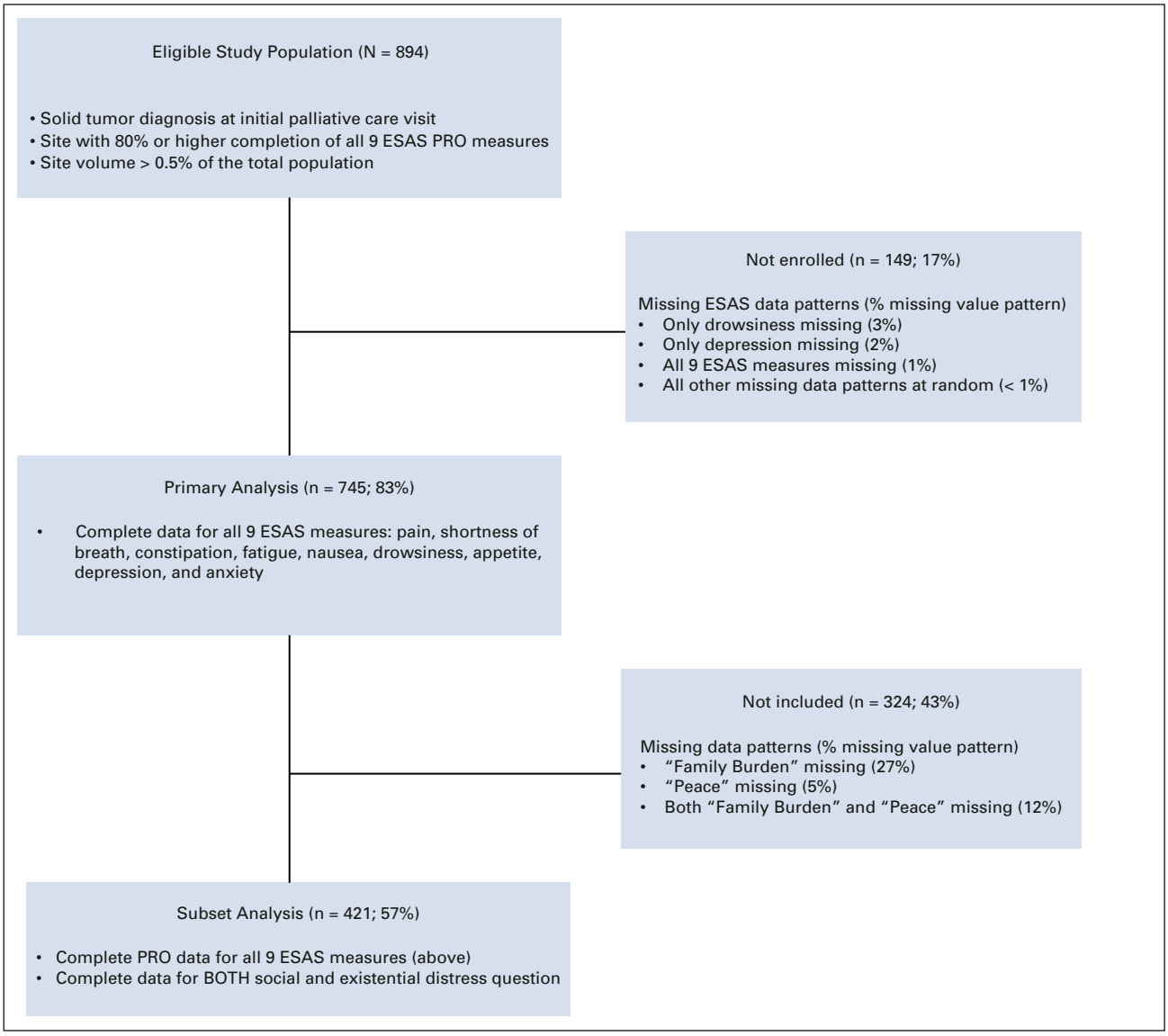

FIG A1. [a]The following answer choices are treated as missing for all ESAS measures and social and existential distress questions: "Unknown", "Unable to Respond", and "Other." ESAS, Edmonton Symptom Assessment System; PRO, patient-reported outcome.

	2 classes	3 classes	4 classes	5 classes	6 classes
AIC	31901.79	31610.08	31399.29	31287.15	31169.62
BIC	32030.97	31785.39	31620.73	31554.72	31483.33
n for each class	C1 = 429	C1 = 259	C1 = 295	C1 = 257	C1 = 216
	C2 = 316	C2 = 343	C2 = 180	C2 = 222	C2 = 176
		C3 = 143	C3 = 201	C3 = 160	C3 = 130
			C4 = 69	C4 = 42	C4 = 152
				C5 = 64	C5 = 39
					C6 = 32

	3-CLASS MODEL		
	Class 1	Class 2	Class 3
Pain	3	5	6
Shortness of Breath	1	3	4
Constipation	1	3	4
Tired	3	6	7
Nausea	1	2	4
Depression	1	2	7
Anxiety	2	3	7
Drowsiness	1	4	5
Appetite	2	5	6
Predicted proportion of total population	0.35	0.45	0.20

	4-CLASS MODEL			
	Class 1	Class 2	Class 3	Class 4
Pain	3	6	5	7
Shortness of Breath	1	2	4	5
Constipation	1	3	3	5
Tired	3	6	7	8
Nausea	1	2	3	6
Depression	1	5	2	7
Anxiety	2	6	3	7
Drowsiness	2	4	4	6
Appetite	2	4	6	7
Predicted proportion of total population	0.39	0.25	0.27	0.09

	5-CLASS MODEL				
	Class 1	Class 2	Class 3	Class 4	Class 5
Pain	3	5	5	6	7
Shortness of Breath	1	2	4	3	5
Constipation	1	3	3	2	5
Tired	3	5	7	7	8
Nausea	1	2	3	1	6
Depression	1	4	1	8	7
Anxiety	1	5	3	8	7
Drowsiness	2	4	5	3	6
Appetite	2	4	6	5	7
Predicted proportion of total population	0.34	0.29	0.22	0.06	0.09

	6-CLASS MODEL					
	Class 1	Class 2	Class 3	Class 4	Class 5	Class 6
Pain	3	5	6	5	6	7
Shortness of Breath	1	2	3	4	3	5
Constipation	1	2	4	3	2	5
Tired	3	4	7	7	7	8
Nausea	1	0	3	2	1	7
Depression	1	4	5	1	8	8
Anxiety	1	4	5	3	7	8
Drowsiness	1	3	5	5	3	7
Appetite	2	3	5	6	4	7
Predicted proportion of total population	0.29	0.23	0.17	0.21	0.05	0.05

FIG A2. Latent profile analysis results. AIC, Akaike information criterion; BIC, Bayesian information criterion.

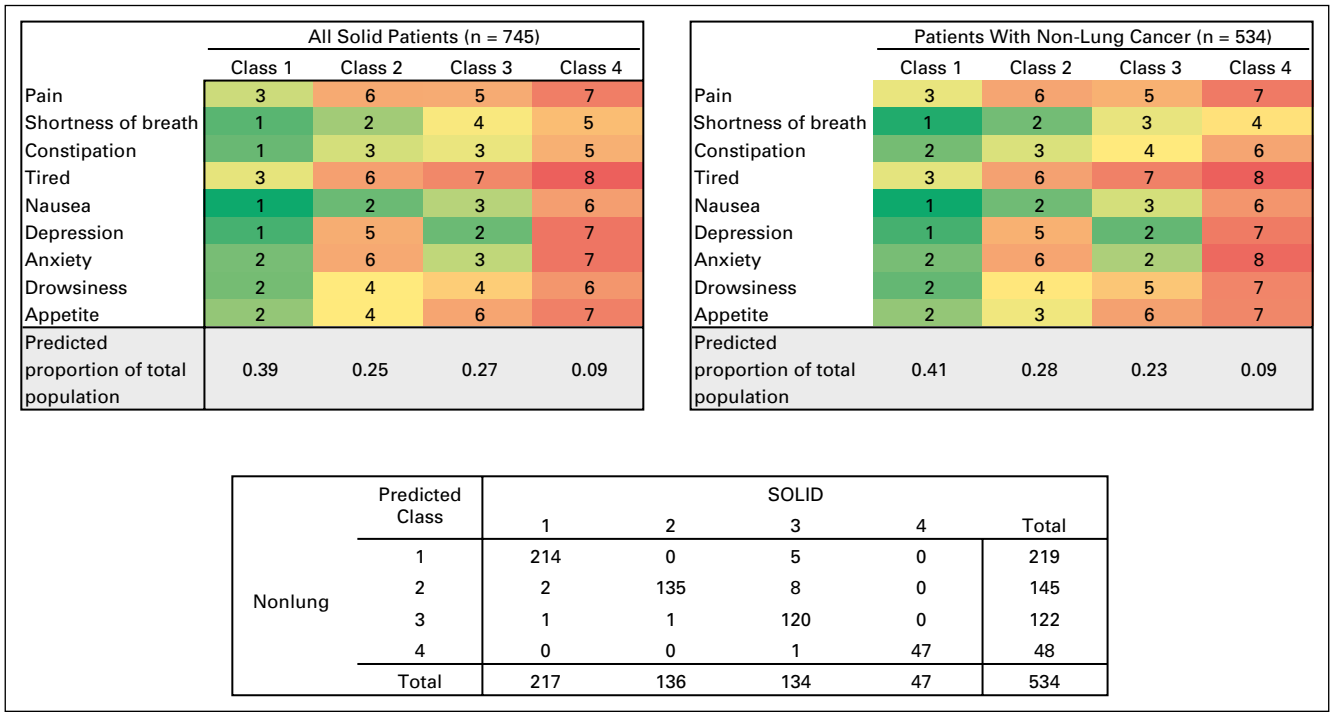

FIG A3. Lung cancer senstivity analysis.

TABLE A1. Existential and Social Distress Items

Question	Answer Options[a]	Derived Binary Variable	Positive Distress Screen
Existential distress measure			
"Are you at peace?"	Not at all	No	×
	A little bit	No	×
	A moderate amount	No	×
	Quite a bit	Yes	
	Completely	Yes	
Social distress measure			
"At times I worry I will be a burden to my family."	Not at all	No	
	A little bit	No	
	A moderate amount	Yes	×
	Quite a bit	Yes	×
	Completely	Yes	×

[a]Answer options also include "unknown" and "patient unable to respond," which are treated as missing in this analysis.

TABLE A2. Comparison of Characteristics for Populations With and Without ESAS Missingness

Characteristic	ESAS With Missingness (n = 149)	ESAS Complete Case (n = 745)	*P*
Age			.43
> 74	34 (22.8%)	148 (19.9%)	
> 55 to 74	60 (40.3%)	306 (41.1%)	
25–55	25 (16.8%)	158 (21.2%)	
Missing	30 (20.1%)	133 (17.9%)	
Age, mean (SD)	65.7 (12.8)	64.1 (13.2)	.22
Sex			.18
Male	56 (37.6%)	226 (30.3%)	
Female	66 (44.3%)	385 (51.7%)	
Missing	27 (18.1%)	134 (18.0%)	
Race			.15
White	94 (63.1%)	521 (69.9%)	
Black	5 (3.4%)	37 (5.0%)	
Others	2 (1.3%)	12 (1.6%)	
Missing	48 (32.2%)	175 (23.5%)	
Relationship status			.06
Married or partner	62 (41.6%)	337 (45.2%)	
Divorced or widowed	25 (16.8%)	127 (17.0%)	
Single or never married	5 (3.4%)	78 (10.5%)	
Missing	57 (38.3%)	203 (27.2%)	
Referring specialty			.21
Oncology	138 (92.6%)	677 (90.9%)	
General medicine	5 (3.4%)	41 (5.5%)	
Others	4 (2.7%)	25 (3.4%)	
Missing	2 (1.3%)	2 (0.3%)	
Palliative Performance Scale (PPS)[a]			.01
PPS ≥ 70	64 (43.0%)	446 (59.9%)	
PPS < 70	66 (44.3%)	285 (38.3%)	
Missing	19 (12.8%)	14 (1.9%)	
Provider prognostic estimation			.007
> 6 Months	41 (27.5%)	336 (45.1%)	
< 6 Months	74 (49.7%)	345 (46.3%)	
Missing	34 (22.8%)	64 (8.6%)	
Cancer type			.20
Lung	46 (30.9%)	211 (28.3%)	
Breast	14 (9.4%)	81 (10.9%)	
Colorectal	14 (9.4%)	49 (6.6%)	
Gynecologic	18 (12.1%)	141 (18.9%)	
Pancreas	9 (6.0%)	51 (6.8%)	
Upper GI liver	8 (5.4%)	57 (7.7%)	
Genitourinary	16 (10.7%)	47 (6.3%)	
Others[b]	23 (15.4%)	106 (14.2%)	
Missing	1 (0.7%)	2 (0.3%)	

(continued on following page)

TABLE A2. Comparison of Characteristics for Populations With and Without ESAS Missingness (continued)

Characteristic	ESAS With Missingness (n = 149)	ESAS Complete Case (n = 745)	*P*
Stage			.36
Metastatic	125 (83.9%)	650 (87.2%)	
Nonmetastatic	23 (15.4%)	95 (12.8%)	
Missing	1 (0.7%)	0 (0.0%)	

Abbreviations: ESAS, Edmonton Symptom Assessment System; SD, standard deviation.

[a]Palliative Performance Scalel (PPS) 70-100 approximately equivalent to Eastern Cooperative Oncology Group 0-1; PPS 40-60 approximately equivalent to Eastern Cooperative Oncology Group 2-3.

[b]Includes thyroid, head and neck, brain, and melanoma.