

Supplemental Table 2. Exemplars of studies that identified subgroups of patients based on a pre-specified symptom cluster

Statistical analysis method	Author, year, and purpose	Disease or chronic condition, sample size, patient characteristics	Symptom assessment instrument(s), symptom dimension(s) used	A prior cluster	Subgroups of patients that were identified based on a symptom cluster	Evaluated for association with a biological mechanism(s)
HCA	<p>Ji et al., 2017¹</p> <p><u>Purpose(s)</u>: Investigate subgroups of symptoms in actively treated patients with cancer based on the measures of pain, fatigue, sleep disturbance, and depression</p> <p>Determine differences in demographic and clinical characteristics among subgroups</p> <p>Examine the relationships between inflammatory cytokines and patient subgroups</p> <p><u>Location</u>: China</p>	<p><u>Disease or condition</u>: advanced gastrointestinal, gynecological, or lung cancer</p> <p><u>n</u> = 170</p> <p>Mean age 56.7 (range 32-77) years</p> <p>Gender Female 57.1% Male 42.9%</p> <p>Race or ethnicity NR</p> <p>Education Primary school 30.6% Middle school 35.3% ≥High school 34.1%</p> <p>Economic status Poor 41.2% Moderate 51.8% Better 7.0%</p>	<p><u>Instrument(s)</u>: Brief Fatigue Inventory Chinese version – 9 items Pain intensity – 0-10 NRS PSQI – 19 items Patient Health Questionnaire Chinese version – 9 items</p> <p><u>Symptom dimension(s)</u>: severity</p>	Pain, fatigue, sleep disturbance, depression	<p>Three subgroups of patients were identified:</p> <ol style="list-style-type: none"> 1. Subgroup 1 - all low symptoms 2. Subgroup 2 - moderate fatigue and low pain subgroup 3. Subgroup 3 - Moderate-to-high on all symptoms 	Serum levels of IL-6, IL-1 β , TNF α
HCA	<p>Li et al., 2019²</p> <p><u>Purpose(s)</u>: Examine the collective effect of a symptom cluster at baseline on the QOL of patients with T2DM over time</p>	<p><u>Disease or condition</u>: T2DM</p> <p><u>n</u> = 302</p> <p>Mean age 63.9 (\pm10.1) years</p> <p>Gender Female 57.6% Male 42.4%</p>	<p><u>Instrument(s)</u>: BDI-II – 21 items Spielberger State-Trait Anxiety Inventory trait subscale – 20 items Symptom Distress Scale – 13 symptoms</p>	Depression, anxiety, fatigue, impaired sleep quality	<p>Four subgroups of patients were identified:</p> <ol style="list-style-type: none"> 1. Subgroup 1 – severe symptoms of fatigue, impaired sleep quality, anxiety, and moderate depression 2. Subgroup 2 – moderate symptoms of fatigue, 	

	<u>Location:</u> United States	Race White 82.5% African American 16.6% Education <4 years college 63.6% >4 years college 32.1% Employment status Employed 30.8% Unemployed/retired/student 69.2%	PSQI – 19 items <u>Symptom dimension(s):</u> severity		impaired sleep quality, and mild symptoms of depression and anxiety 3. Subgroup 3 – moderate symptoms of fatigue, impaired sleep quality, anxiety, and mild depression 4. Subgroup 4 – low symptoms of fatigue, depression, anxiety, and mild impaired sleep quality	
HCA	Park & Larson, 2014 ³ <u>Purpose(s):</u> Determine how subgroups of patients with COPD, identified by their ratings of symptoms (dyspnea, anxiety, depression, fatigue), differed on healthcare use and mortality <u>Location:</u> data from United States	<u>Disease or condition:</u> COPD <i>n</i> = 597 Mean age 65.9 (±10.2) years Gender Male 63.5% Race White 94.1% Education ≥College degree 50.9% Income ≥\$30,000 47.5%	<u>Instrument(s):</u> University of California, San Diego, Shortness of Breast Questionnaire – 24 items Spielberger State-Trait Anxiety Inventory state subscale – 20 items BDI – 21 items Short-Form Health Survey – 36 symptoms <u>Symptom dimension(s):</u> severity	Dyspnea, anxiety, depression, fatigue	Three subgroups of patients were identified: 1. All low symptom subgroup 2. Moderate symptom subgroup 3. All high symptom subgroup	
Group-based multitrajectory modeling	Li et al., 2020 ⁴ <u>Purpose(s):</u> Identify subgroups of women with breast cancer with the psychological symptom cluster (i.e., fatigue, depressive symptoms, anxiety) during the first 18	<u>Disease or condition:</u> breast cancer <i>n</i> = 292 Low Severity Group Mean age 61.9 (±6.2) years Gender Female 100%	<u>Instrument(s):</u> Profile of Mood States Fatigue/Inertial subscale – 7 items Profile of Mood States Tension/Anxiety subscale – 9 items	Fatigue, depressive symptoms, anxiety	Two subgroups of patients were identified: 1. Low group – severity of fatigue and depressive symptoms remained low from baseline to 18 months, and anxiety declined from baseline to 18 months	Genetic polymorphisms related to hypothalamic-pituitary-adrenal axis function

	<p>months of adjuvant therapy</p> <p>Explore associations between demographic and clinical characteristics and variations in genetic polymorphisms related to hypothalamic-pituitary-adrenal axis function</p> <p><u>Location</u>: United States</p>	<p>Race or ethnicity White 96.9% Black 3.1%</p> <p>Education Mean 15.2 (± 2.9) years</p> <p>Employment NR</p> <p>High Severity Group Mean age 58.7 (± 5.3) years</p> <p>Gender Female 100%</p> <p>Race or ethnicity White 95.5% Black 4.5%</p> <p>Education Mean 14.0 (± 2.2) years</p> <p>Employment NR</p>	<p>BDI-II – 21 items</p> <p><u>Symptom dimension(s)</u>: severity</p>		<p>2. High group – severity of fatigue and depressive symptoms were high from baseline to 18 months, and severity of anxiety was high at baseline, decreased from baseline to six months, then increased after 12 months</p>	
LCA	<p>Conley et al., 2017⁵</p> <p><u>Purpose(s)</u>: Identify symptom cluster membership groups for symptoms of pain, fatigue, sleep disturbance, depression, and anxiety, among adults with IBD</p> <p>Examine the associations between demographic and clinical factors, and membership in specific symptom clusters</p>	<p><u>Disease or condition</u>: IBD</p> <p>$n = 5296$</p> <p>Mean age 44.1 (± 15.2) years</p> <p>Gender Female 72.1% Male 27.9%</p> <p>Race or ethnicity White non-Hispanic 92.3% Other 7.7%</p> <p>Education \leqHigh school 7% Some college/college degree 55.4%</p>	<p><u>Instrument(s)</u>: PROMIS measures of pain, fatigue, sleep disturbance, depression, anxiety – 4 items</p> <p><u>Symptom dimension(s)</u>: occurrence</p>	Pain, fatigue, sleep disturbance, depression, anxiety	<p>Three classes of patients were identified:</p> <ol style="list-style-type: none"> 1. Low symptom burden class 2. High symptom burden class 3. Physical symptoms class 4. Psychological symptoms class 	

	Location: United States	Graduate school 29% Employment or income NR				
LCA	<p>Cray et al., 2010⁶</p> <p><u>Purpose(s)</u>: Identify groups of women in the late menopausal transition stage who experienced the same cluster of symptoms</p> <p>Identify indicators that predicted membership in these distinct groups</p> <p>Location: United States</p>	<p><u>Disease or condition</u>: late stage of menopause</p> <p>$n = 103$</p> <p>Mean age 42.3 (± 4.6) years</p> <p>Gender Female 100%</p> <p>Race or ethnicity White 88.3% Asian/Pacific Islander 6.3% African American 2.9% Other (Hispanic, mixed) 1.9%</p> <p>Education Mean 15.9 (± 3.0) years</p> <p>Employed Yes 90.3% No 9.7%</p>	<p><u>Instrument(s)</u>: Health diary – 47 symptoms</p> <p><u>Symptom dimension(s)</u>: severity</p>	Problem concentrating, hot flashes, joint ache, mood changes, awakening at night	<p>Four groups of women were identified:</p> <ol style="list-style-type: none"> 1. All low symptom group - low severity for all symptoms except for joint ache 2. All high symptom group - high severity for all symptoms, except moderate for hot flashes 3. High hot flashes, joint ache, and awakening at night symptom group - high severity for hot flashes, joint ache, and awakening at night 4. High problem concentrating, joint ache severity group - high severity for problem concentrating and joint ache 	Urine levels of estrone glucuronide, follicle-stimulating hormone, and cortisol
LCA	<p>Finlayson et al., 2017⁷</p> <p><u>Purpose(s)</u>: Identify patient subgroups based on their experience with a pain-depression-fatigue-sleep disturbance symptom cluster</p> <p>Identify differences in patient characteristics and wound-healing and QOL outcomes between the subgroups</p>	<p><u>Disease or condition</u>: venous leg ulcers</p> <p>$n = 247$</p> <p>Mean age 69.1 (± 14.7) years</p> <p>Gender Female 49% Male 51%</p> <p>Race or ethnicity NR</p> <p>Education NR</p>	<p><u>Instrument(s)</u>: Medical Outcomes Study Pain Measure – 7 items Geriatric Depression Scale-Short Form – 15 items Short Form-12 Vitality subscale – 1 item Cardiff Wound Impact Schedule Disturbed Sleep – 1 item</p>	Pain, depression, fatigue, sleep disturbance	<p>Two subgroups of patients were identified:</p> <ol style="list-style-type: none"> 1. Mild symptom subgroup - mild pain, no or mild depressive symptoms and fatigue, mild-to-moderate sleep disturbance 2. Severe symptom subgroup - moderate-to-severe pain, depressive symptoms, sleep disturbance, and fatigue 	

	<u>Location</u> : Australia	Employment NR	<u>Symptom dimension(s)</u> : severity			
LCA	<p>Saravanan et al., 2021⁸</p> <p><u>Purpose(s)</u>: Identify behavioral symptom clusters (i.e., depressive mood, fatigue, poor sleep) in individuals with chronic low back pain</p> <p>Determine whether differences exist in pain, QOL, and inflammation based on cluster membership</p> <p><u>Location</u>: United States</p>	<p><u>Disease or condition</u>: chronic low back pain</p> <p>$n = 69$</p> <p>Mean age 55.8 (± 12.9) years</p> <p>Gender Female 73.9% Male 26.1%</p> <p>Race or ethnicity White 58.0% Hispanic 20.3% African American 15.9% Asian/Pacific Islander 5.8%</p> <p>Education NR</p> <p>Employment or income NR</p>	<p><u>Instrument(s)</u>: BPI – 1 item Center for Epidemiological Studies- Depression scale – 20 items PSQI – 19 items</p> <p><u>Symptom dimension(s)</u>: severity</p>	Depressive mood, fatigue, poor sleep	Two classes of patients were identified:	Plasma levels of IL-6
Multilevel LCA	<p>Woods et al., 2018⁹</p> <p><u>Purpose(s)</u>: Test associations between symptom clusters identified through latent class analysis and polymorphisms in the estrogen synthesis pathway genes</p> <p><u>Location</u>: United States</p>	<p><u>Disease or condition</u>: women in late reproductive stage, early or late menopausal transition, or early post-menopause</p> <p>$n = 137$</p> <p>Mean age 40.9 (± 3.9) years</p> <p>Gender Female 100%</p> <p>Race or ethnicity Caucasian 87.8% Asian/Pacific Islander 8.6% African American 2.9%</p>	<p><u>Instrument(s)</u>: Health diary – 47 symptoms</p> <p><u>Symptom dimension(s)</u>: severity</p>	Sleep, pain, mood, cognitive, tension, hot flash	Three clusters of patients were identified:	Polymorphisms in estrogen synthesis pathway genes

		Other (Hispanic, mixed) 0.7% Education Mean 16.1 (\pm 3.9) years Employed Yes 85.7% Family Income Mean \$39,800 (\pm \$15,000)				
--	--	---	--	--	--	--

Abbreviations: BDI-II = Beck Depression Inventory-II; BPI = Brief Pain Inventory; COPD = chronic obstructive pulmonary disease; HCA = hierarchical cluster analysis; IBD = irritable bowel disease; IL-6 = interleukin-6; LCA = latent class analysis; LPA = latent profile analysis; PROMIS = Patient Reported Outcomes Measurement Information System; PSQI = Pittsburgh Sleep Quality Index; QOL = quality of life; T2DM = type 2 diabetes mellitus

References

1. Ji YB, Bo CL, Xue XJ, et al. Association of inflammatory cytokines with the symptom cluster of pain, fatigue, depression, and sleep disturbance in Chinese patients with cancer. *J Pain Symptom Manage*. Dec 2017;54(6):843-852. doi:10.1016/j.jpainsymman.2017.05.003
2. Li H, Ji M, Scott P, Dunbar-Jacob JM. The effect of symptom clusters on quality of life among patients with type 2 diabetes. *Diabetes Educ*. Jun 2019;45(3):287-294. doi:10.1177/0145721719837902
3. Park SK, Larson JL. Symptom cluster, healthcare use and mortality in patients with severe chronic obstructive pulmonary disease. *J Clin Nurs*. Sep 2014;23(17-18):2658-71. doi:10.1111/jocn.12526
4. Li HJ, Marsland AL, Conley YP, Sereika SM, Bender CM. Genes involved in the HPA axis and the symptom cluster of fatigue, depressive symptoms, and anxiety in women with breast cancer during 18 months of adjuvant therapy. *Biol Res Nurs*. Apr 2020;22(2):277-286. doi:10.1177/1099800419899727
5. Conley S, Proctor DD, Jeon S, Sandler RS, Redeker NS. Symptom clusters in adults with inflammatory bowel disease. *Res Nurs Health*. Oct 2017;40(5):424-434. doi:10.1002/nur.21813
6. Cray L, Woods NF, Mitchell ES. Symptom clusters during the late menopausal transition stage: observations from the Seattle Midlife Women's Health Study. *Menopause*. 2010;17(5):972-977. doi:10.1097/gme.0b013e3181dd1f95
7. Finlayson K, Miaskowski C, Alexander K, et al. Distinct wound healing and quality-of-life outcomes in subgroups of patients with venous leg ulcers with different symptom cluster experiences. *J Pain Symptom Manage*. May 2017;53(5):871-879. doi:10.1016/j.jpainsymman.2016.12.336
8. Saravanan A, Bajaj P, Mathews HL, Tell D, Starkweather A, Janusek L. Behavioral symptom clusters, inflammation, and quality of life in chronic low back pain. *Pain Manage Nurs*. 2021;22(3):361-368. doi:10.1016/j.pmn.2020.11.012
9. Woods NF, Cray LA, Mitchell ES, Farrin F, Herting J. Polymorphisms in estrogen synthesis genes and symptom clusters during the menopausal transition and early postmenopause: Observations from the Seattle Midlife Women's Health Study. *Biol Res Nurs*. Mar 2018;20(2):153-160. doi:10.1177/1099800417753536