

Supplemental Table 1. Exemplars of studies that identified symptom clusters de novo

Statistical analysis method	Author, year, and purpose	Disease or chronic condition, sample size, patient characteristics	Symptom assessment instrument(s), symptom dimension(s) used	Symptom clusters and specific symptoms within each cluster	Evaluated for association with a biological mechanism(s)
HCA	Galain et al., 2018 ¹ <u>Purpose(s)</u> : Assess the prevalence of symptoms, identify symptom clusters, and describe the impact of concurrent symptoms on physical and emotional well-being in a sample of dialysis patients <u>Location</u> : Uruguay	<u>Disease or condition</u> : ESRD $n = 493$ Mean age 60.9 (± 16.7) years Gender Female 43.6% Male 56.4% Race or ethnicity NR Education <Primary school 2.3% Primary school 37.2% <High school 40.5% High school 13.8% College/university 6.2% Employment Full time 10.6% Part time 7.6% Retired 66.6% Social welfare 0.2% Unemployed 2.7% Medical leave 2.5% Other 9.8%	<u>Instrument(s)</u> : Kidney Disease QOL – 36 items Hospital Anxiety and Depression Scale – 14 items Pain assessed using a visual analogue scale Epworth Sleepiness Scale – 8 items <u>Symptom dimension(s)</u> : severity	Five “first-level” symptom clusters were identified: <u>Cutaneous cluster</u> : dry skin, itch <u>Neuropathic cluster</u> : numbness, cramps <u>Energy cluster</u> : washed out, faintness <u>Digestive cluster</u> : nausea, lack of appetite <u>Cardiac cluster</u> : shortness of breath, chest pain Three “intermediate-, second-, and third-level” symptom clusters were identified: <u>Intermediate</u> : washed out, faintness, muscle soreness <u>Neuromuscular</u> : numbness, cramps, washed out, faintness, muscle soreness <u>Uremic</u> : Numbness, cramps, washed out, faintness, muscle soreness, nausea, lack of appetite	
HCA	Garcia et al., 2019 ² <u>Purpose(s)</u> : Identify the most common symptoms experienced by Mexican American adults with T2DM	<u>Disease or condition</u> : T2DM $n = 71$ Mean age 49.5 (± 9.1) years Gender Female 66%	<u>Instrument(s)</u> : Diabetes Symptom Self-Management Inventory symptom subscale – 38 items <u>Symptom dimension(s)</u> : unclear	Three unnamed symptom clusters were identified: <u>Cluster 1</u> : sweating, intense thirstiness, urinating more than usual, cravings, dry mouth, tiredness, numbness or tingling, problems with sleeping, dry skin	

	<p>Analyze differences among sex, acculturation, education, time since diagnosis, number of comorbid conditions, number of medications, hemoglobin A1c, body mass index, blood pressure, QOL, and symptom burden</p> <p>Explore how diabetes symptoms cluster together</p> <p><u>Location:</u> United States</p>	<p>Male 44%</p> <p>Ethnicity Mexican American 100%</p> <p>Languages read and spoken Only Spanish or Spanish better than English 44% Both equally 11% Only English or English better than Spanish 44%</p> <p>Education 12.3 (\pm4.3) years</p> <p>Employed Full time 51%</p>		<p><u>Cluster 2:</u> itching skin, weight gain, discolored skin areas, noise or light sensitivity, trembling, flushing, sexual problems, burning in feet or legs, hair loss</p> <p><u>Cluster 3:</u> constipation, dizziness, indigestion or nausea, sadness, irritability, easily angry, nervous, fidgety, weakness, anxiousness, headache, trouble concentrating, memory loss</p>	
HCA	<p>Lee et al., 2010³</p> <p><u>Purpose(s):</u> Compare symptom clusters between men and women with HF</p> <p>Evaluate for differences in patient characteristics among symptom clusters</p> <p>Evaluate the impact of symptom clusters on cardiac event-free survival</p> <p><u>Location:</u> United States</p>	<p><u>Disease or condition:</u> HF</p> <p>$n = 331$</p> <p>Mean age 61 (\pm11) years</p> <p>Gender Female 66% Male 44%</p> <p>Ethnicity White 81%</p> <p>Education NR</p> <p>Employment NR</p>	<p><u>Instrument(s):</u> Minnesota Living with Heart Failure Questionnaire – 21 items</p> <p><u>Symptom dimension(s):</u> distress</p>	<p>Two symptom clusters were identified in both men and women:</p> <p><u>Physical cluster:</u> dyspnea, fatigue/increased need to rest, fatigue/low energy, sleep disturbances</p> <p><u>Emotional/cognitive cluster:</u> worrying, feeling depressed, cognitive problems</p>	
HCA	<p>Stapleton et al., 2016⁴</p> <p><u>Purpose(s):</u> Identify symptom clusters based on item ratings from the SDS</p> <p>Examine symptom clusters for differences</p>	<p><u>Disease or condition:</u> cancer in the hospice or palliative care setting</p> <p>$n = 150$</p> <p>Mean age 59 (\pm13) years</p> <p>Gender</p>	<p><u>Instrument(s):</u> SDS – 13 items</p> <p><u>Symptom dimension(s):</u> distress for 11 items; severity for 2 items</p>	<p>Four symptom clusters were identified:</p> <p><u>Pain-fatigue:</u> pain frequency, fatigue, pain intensity</p> <p><u>Ingestion-elimination:</u> appetite and bowel problems</p>	

	<p>by gender, race/ethnicity, analgesic consumption, and sleep quality</p> <p><u>Location</u>: United States</p>	<p>Female 58.7% Male 41.3%</p> <p>Race or ethnicity Caucasian 37.3% African American 51.3% Hispanic 6.0% Asian 2.0% Native American 0.7% Other 2.7%</p> <p>Education ≤8th grade 10.0% ≤12th grade 38.7% Vocational 14.0% Associate's degree 15.3% Bachelor's degree 9.3% Master's degree 5.3% Doctoral degree 2.0% Unknown 5.3%</p> <p>Income <\$10,000 34.7% \$10-20,000 18.0% \$21-30,000 7.3% \$31-40,000 7.3% \$41-50,000 10.7% >\$50,000 9.3% <u>Unknown</u> 12.7%</p>		<p><u>General well-being</u>: insomnia, appearance, outlook</p> <p><u>Respiratory-nausea-concentration</u>: breathing, cough, nausea frequency, nausea intensity, concentration</p>	
HCA	<p>Steur et al., 2017⁵</p> <p><u>Purpose(s)</u>: Determine the number of symptom clusters present among adults with chronic atrial fibrillation</p> <p>Explore sociodemographic and clinical factors potentially associated with cluster membership</p> <p><u>Location</u>: Australia</p>	<p><u>Disease or condition</u>: atrial fibrillation'</p> <p>$n = 335$</p> <p>Mean age 72 (±11.3) years</p> <p>Gender Female 48% Male 52%</p> <p>Ethnicity European/white 96.4% Aboriginal/Torres Strait Islander 1.2%</p>	<p><u>Instrument(s)</u>: Atrial fibrillation profiling instrument (modified)– 8 symptoms</p> <p><u>Symptom dimension(s)</u>: occurrence</p>	<p>Three symptom clusters were identified using occurrence:</p> <p><u>Vagal cluster</u>: nausea, diaphoresis</p> <p><u>Tired cluster</u>: fatigue/lethargy, weakness, syncope/dizziness, dyspnea/breathlessness</p> <p><u>Heart cluster</u>: chest pain/discomfort, palpitations/fluttering</p>	

		<p>Asian 1.5% Middle Eastern 0.9%</p> <p>Education NR</p> <p>Living alone Yes 39.4%</p> <p>Income or employment NR</p>			
EFA	<p>Almutary et al., 2016⁶</p> <p><u>Purpose(s)</u>: Explore symptom clusters based on different symptom dimensions (occurrence, frequency, distress) in the most burdensome stages of CKD</p> <p><u>Location</u>: Australia</p>	<p><u>Disease or condition</u>: CKD</p> <p>$n = 436$</p> <p>Mean age 48.3 (± 14.9) years</p> <p>Gender Female 47% Male 53%</p> <p>Race or Ethnicity NR</p> <p>Education ≤Secondary 53.9% Secondary 24.1% College or above 21.6%</p> <p>Employment status Employed 50.9% Unemployed 29.8% Retired 19.3%</p>	<p><u>Instrument(s)</u>: CKD Symptom Burden Index – 32 symptoms</p> <p><u>Symptom dimension(s)</u>: occurrence, severity, frequency, distress</p>	<p>Five symptom clusters were identified across occurrence, severity, frequency, and distress:</p> <p>Occurrence <u>Fluid volume symptoms</u>: dry skin, itching, cough, shortness of breath, chest pain, lightheadedness or dizziness, difficulty concentrating, dry mouth, swelling in legs, bone or joint pain</p> <p><u>Neuromuscular symptoms</u>: muscle soreness, muscle cramps, numbness or tingling in feet</p> <p><u>Sexual symptoms</u>: decreased interest in sex, difficulty becoming sexually aroused</p> <p><u>Psychological symptoms</u>: feeling anxious, worrying, feeling sad, depression, feeling nervous, irritability</p> <p><u>Gastrointestinal symptoms</u>: vomiting, nausea, decreased appetite</p> <p>Severity <u>Fluid volume symptoms</u>: cough, shortness of breath, chest pain, lightheadedness or dizziness, difficulty concentrating, decreased appetite</p> <p><u>Neuromuscular symptoms</u>: muscle soreness, muscle cramps, numbness or tingling in feet, restless leg, bone or joint pain, trouble falling asleep, feeling tired or lack of energy</p>	

				<p><u>Sexual symptoms</u>: decreased interest in sex, difficulty becoming sexually aroused</p> <p><u>Psychological symptoms</u>: feeling anxious, worrying, feeling sad, depression, feeling nervous</p> <p><u>Gastrointestinal symptoms</u>: vomiting, nausea, diarrhea</p> <p>Frequency <u>Fluid volume symptoms</u>: itching, cough, shortness of breath, chest pain, lightheadedness or dizziness, difficulty concentrating, trouble staying asleep, restless leg</p> <p><u>Neuromuscular symptoms</u>: muscle soreness, muscle cramps, numbness or tingling in feet, bone or joint pain</p> <p><u>Sexual symptoms</u>: decreased interest in sex, difficulty becoming sexually aroused</p> <p><u>Psychological symptoms</u>: feeling anxious, worrying, feeling sad, depression, feeling nervous</p> <p><u>Gastrointestinal symptoms</u>: vomiting, nausea</p> <p>Distress <u>Fluid volume symptoms</u>: dry skin, itching, cough, shortness of breath, chest pain, lightheadedness or dizziness, difficulty concentrating, dry mouth, trouble falling asleep, headache</p> <p><u>Neuromuscular symptoms</u>: muscle soreness, numbness or tingling in feet, restless leg</p> <p><u>Sexual symptoms</u>: decreased interest in sex, difficulty becoming sexually aroused</p>	
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EFA	<p>Du et al., 2021⁷</p> <p><u>Purpose(s)</u>: Explore the symptom clusters in renal transplant recipients</p> <p><u>Location</u>: China</p>	<p><u>Disease or condition</u>: renal transplant</p> <p>$n = 295$</p> <p>Mean age 45.0 (± 12.2) years</p> <p>Gender Female 38% Male 62%</p> <p>Race or Ethnicity NR</p> <p>Education \leqMiddle school 26.8% High school or technical secondary school 40.0% \geqCollege degree 34.2%</p> <p>Employed Yes 31.9% No 68.1%</p> <p>Family income per month in RMB <3,000 53.2% <u>3,000-6,000 30.5%</u> <u>6,001-10,000 9.8%</u> <u>>10,000 6.4%</u></p> <p>Economic burden No burden 7.8% Mild 10.5% Moderate 32.5% Severe 49.2%</p>	<p><u>Instrument(s)</u>: Transplant Symptoms and Disturbance Scale-59R (modified) – 62 symptoms</p> <p><u>Symptom dimension(s)</u>: severity</p>	<p>Five unnamed symptom clusters were identified:</p> <p><u>Cluster 1</u>: anxiety, restlessness/nervousness, depression, mood swings, nightmares, sleep difficulties, palpitations</p> <p><u>Cluster 2</u>: chest pain, back pain, wind, diarrhea, muscle soreness, stomach complaints/nausea/vomiting, joint pain</p> <p><u>Cluster 3</u>: swollen gums, brittle fingernails, bruises, sores on lips or in mouth, tiredness</p> <p><u>Cluster 4</u>: poor appetite, changed sense of taste, constipation, lack of energy, brittle skin</p> <p><u>Cluster 5</u>: difficulty seeing well, sensitivity to light, muscle cramps</p>	

EFA	<p>Edwards et al., 2014⁸</p> <p><u>Purpose(s)</u>: Identify the prevalence and severity of common symptoms and the occurrence of symptom clusters in patients with venous leg ulcers</p> <p><u>Location</u>: Australia</p>	<p><u>Disease or condition</u>: chronic venous leg ulcers</p> <p>$n = 318$</p> <p>Mean age 70 (± 14.6) years</p> <p>Gender Female 51% Male 49%</p> <p>Race or Ethnicity NR</p> <p>Education NR</p> <p>Income Age pension 70% Disability pension 15% Employed or self-funded 12%</p>	<p><u>Instrument(s)</u>: Medical Outcomes Study Pain Measures – 7 items Geriatric Depression Scale – 15 items Cardiff Wound Impact Schedule physical symptoms scale Short Form-12 Health Survey Questionnaire - 12 items</p> <p><u>Symptom dimension(s)</u>: severity</p>	<p>Two symptom clusters were identified:</p> <p><u>Pain/fatigue cluster</u>: pain, fatigue, depression, sleep disturbance</p> <p><u>Inflammation cluster</u>: inflammation, swelling/edema, fatigue, exudate</p>	
FA	<p>Fu et al., 2009⁹</p> <p><u>Purpose(s)</u>: Assess the prevalence of persistent physical and emotional symptoms and identify sociodemographic factors associated with these symptoms in a cohort of predominantly Hispanic and white breast cancer survivors</p> <p><u>Location</u>: United States</p>	<p><u>Disease or condition</u>: breast cancer</p> <p>$n = 139$</p> <p>Median age 52.5 (range 26-90) years</p> <p>Gender Female 100%</p> <p>Race or ethnicity Non-Hispanic white 42% Hispanic 45% Non-Hispanic black 13%</p> <p>Primary language English 58% Spanish 39% Other 3%</p> <p>Education</p>	<p><u>Instrument(s)</u>: Modified version of the MSAS-Short Form – 16 items</p> <p><u>Symptom dimension(s)</u>: NR</p>	<p>Four symptom clusters were identified:</p> <p><u>Depression</u>: sadness/depression, anxiety, grief/loss</p> <p><u>Hormone</u>: fatigue, poor sex drive, hot flashes, headache, poor memory</p> <p><u>Chemotherapy</u>: poor appetite, nausea, lymphedema, neuropathy</p> <p><u>Pain</u>: insomnia, muscle aches, bone pain</p>	

		<p><High school graduate 22%</p> <p>High school graduate 22%</p> <p>Post-high school 56%</p> <p>Annual household income</p> <p><\$10,000 27%</p> <p>\$10,000-49,999 20%</p> <p>\$50,000-100,000 25%</p> <p>>\$100,000 12%</p> <p>Not reported 15%</p>			
EFA	<p>Hao et al., 2021¹⁰</p> <p><u>Purpose(s)</u>: Identify the symptoms experienced by COPD patients and classify them into symptom clusters based on different symptom dimensions</p> <p>Assess the quality of sleep in patients with COPD and compare to symptom and QOL</p> <p>Determine the effects of sleep quality and symptom clusters on the QOL of COPD patients</p> <p><u>Location</u>: China</p>	<p><u>Disease or condition</u>: COPD</p> <p>$n = 223$</p> <p>Mean age 65.2 (± 5.6) years</p> <p>Gender</p> <p>Female 31.8%</p> <p>Male 68.2%</p> <p>Education</p> <p>\leqHigh school degree 90.1%</p> <p>College graduate 8.5%</p> <p>Employment status</p> <p>Employed 17.9%</p> <p>Unemployed 82.1%</p> <p>Family income per month in RMB</p> <p><2,000 8.5%</p> <p>2,000-4,999 73.9%</p> <p>$\geq 5,000$ 18.3%</p>	<p><u>Instrument(s)</u>: Revised MSAS Chinese version – 19 symptoms</p> <p><u>Symptom dimension(s)</u>: severity</p>	<p>Three symptom clusters were identified using severity:</p> <p><u>Respiratory functional cluster</u>: cough, shortness of breath, dry mouth, feeling bloated, problems with sexual interest or activity</p> <p><u>Emotional cluster</u>: worrying, feeling sad, feeling nervous, feeling irritable, “I do not look like myself”</p> <p><u>Fatigue-sleep cluster</u>: difficulty sleeping, lack of energy, feeling drowsy</p>	
EFA	<p>Hu et al., 2021¹¹</p> <p><u>Purpose(s)</u>: Identify symptom clusters among Chinese patients with chronic HF and examine their</p>	<p><u>Disease or condition</u>: HF</p> <p>$n = 201$</p> <p>Mean age 65.9 (± 10.7) years</p> <p>Gender</p>	<p><u>Instrument(s)</u>: MSAS-HF Chinese version – 32 items</p> <p><u>Symptom dimension(s)</u>: severity</p>	<p>Six symptom clusters were identified using severity:</p> <p><u>Fatigue cluster</u>: lack of energy, sleep difficulties, lack of appetite</p>	

	<p>independent relationships with QOL</p> <p><u>Location</u>: China</p>	<p>Female 47.3% Male 52.7%</p> <p>Race or ethnicity NR</p> <p>Education ≤Elementary school 46.8% Middle school 28.9% High school 13.9% University or higher 10.5%</p> <p>Employment status Employed 23.4% Unemployed 76.6%</p>		<p><u>Dyspneic cluster</u>: waking up breathless at night, difficulty breathing when lying flat, shortness of breath</p> <p><u>Discomfort cluster</u>: sleepiness, dry mouth, sweating</p> <p><u>Congestive cluster</u>: cough, swollen legs or ankles, bloating, nausea, abnormal urination</p> <p><u>Ischemic cluster</u>: dizziness, palpitations, chest pain</p> <p><u>Emotional cluster</u>: nervousness, anxiety, sadness</p>	
EFA	<p>Kelechi et al., 2017¹²</p> <p><u>Purpose(s)</u>: Determine whether there are differences between women and men in the 11 symptoms of chronic venous disease</p> <p>Determine whether there are symptom clusters for the overall sample</p> <p>Determine whether there are differences in symptom clusters between men and women</p> <p>Determine whether there are differences in symptom clusters between men and women with and without venous leg ulcers in the past 2 years</p> <p><u>Location</u>: United States</p>	<p><u>Disease or condition</u>: chronic venous disease</p> <p><i>n</i> = 264</p> <p>Mean age 61.7 (±11.9) years</p> <p>Gender Female 54.5% Male 45.5%</p> <p>Race Black 58.0% White 42.0%</p> <p>Education ≤8th grade 7.6% Some high school 15.2% High school graduate 36.4% Some college 23.5% College graduate 17.4%</p> <p>Employment status Full time 23.1% Volunteer, employed part time, homemaker, student 10.2%</p>	<p><u>Instrument(s)</u>: VEINS-SYM subscale of the VEINES-QOL questionnaire– 11 items</p> <p><u>Symptom dimension(s)</u>: severity</p>	<p>Two symptom clusters were identified in the total sample using severity:</p> <p><u>Distressful cluster</u>: aching legs, night cramps, throbbing, irritable, pain</p> <p><u>Discomfort cluster</u>: heavy legs, burning, tingling</p> <p>Two symptom clusters were identified among women using severity:</p> <p><u>Hurting cluster</u>: aching legs, throbbing, itching, irritable, pain</p> <p><u>Annoying cluster</u>: heavy legs, burning, tingling</p> <p>Two symptom clusters were identified among men using severity:</p> <p><u>Nagging cluster</u>: heavy legs, aching legs, restlessness, throbbing, pain</p> <p><u>Irritating cluster</u>: burning, itching, tingling</p>	

		Retired 48.9% Unemployed 17.8%			
EFA	<p>Makhani et al., 2011¹³</p> <p><u>Purpose(s)</u>: Conduct a factor analysis on a large database of IBS patients who had breath testing to explore the relationship between the frequency of various GI symptoms and the presence or absence of methane among IBS patients</p> <p><u>Location</u>: United States</p>	<p><u>Disease or condition</u>: IBS</p> <p>Methane <i>n</i> = 72 Nonmethane <i>n</i> = 387</p> <p>Sample characteristics not reported</p>	<p><u>Instrument(s)</u>: Unknown questionnaire – 31 GI symptoms</p> <p><u>Symptom dimension(s)</u>: severity</p>	<p>Identified six named and unnamed methane clusters:</p> <p><u>Bloating cluster</u>: bloating, bloating with meals, gas, milk intolerance, joint pain, incomplete evacuation, rumbling</p> <p><u>Pain cluster</u>: pain with bowel movement, pain after bowel movement, mucus, straining</p> <p><u>Cluster 3</u>: joint pain, backache, fatigue, foul-smelling stool, large bowel movements, weak after bowel movement</p> <p><u>Cluster 4</u>: fruit intolerance, heartburn, vomiting, pain at night</p> <p><u>Cluster 5</u>: blood in stool, black stool, urgency</p> <p><u>Constipation cluster</u>: – constipation, milk intolerance, weight loss, small bowel movements, straining</p> <p>Identified two non-methane clusters:</p> <p><u>Bloating cluster</u>: bloating, bloating with meals, bloating on waking, constipation, heartburn, backache, small bowel movements, incomplete evacuation, straining</p> <p><u>Diarrhea cluster</u>: diarrhea, pain with bowel movement, pain after bowel movement, foul-smelling stool, large bowel movements, weak after bowel movement, urgency</p>	
EFA, CFA	<p>Min et al., 2021¹⁴</p> <p><u>Purpose(s)</u>: Identify and compare the number and types of symptom clusters based on two symptom dimensions – symptom occurrence</p>	<p><u>Disease or condition</u>: metabolic syndrome in midlife menopausal women</p> <p>Midlife menopausal women with metabolic syndrome <i>n</i> = 424</p>	<p><u>Instrument(s)</u>: CES-D scale – 1 symptom Study of Women's Health Across the Nation questionnaire – 14 symptoms</p>	<p>Three symptom clusters were identified across occurrence and severity using EFA and were confirmed using CFA:</p> <p>Occurrence symptom clusters <i>Women with metabolic syndrome</i> <u>Mental health cluster</u>: depression, anxiety, frequent mood changes, forgetfulness</p>	

	<p>and symptom severity – in midlife menopausal women with metabolic syndrome and without metabolic syndrome</p> <p><u>Location</u>: United States</p>	<p>Mean age 46.5 (\pm2.8) years</p> <p>Race or ethnicity White 43.9% African American 37.0% Chinese 3.8% Japanese 4.3% Hispanic 11.1%</p> <p>Education <High school 10.3% High school graduate 24.0% Some college/technical 38.4% College graduate 10.8% Post-graduate education 16.6%</p> <p>Employment Currently working 73.1%</p> <p>Annual household income <\$19,999 23.8% \$20,000-49,999 34.7% \$50,000-99,999 31.1% \geq\$100,000 7.3%</p> <p>Difficulty paying for basics Very hard 13.9% Somewhat hard 38.4% Not very hard at all 47.6%</p> <p>Without metabolic syndrome <i>n</i> = 1022</p> <p>Mean age 46.1 (\pm2.7) years</p> <p>Race or ethnicity White 50.8% African American 27.9% Chinese 7.4%</p>	<p><u>Symptom dimension(s)</u>: occurrence, severity</p>	<p><u>Vasomotor cluster</u>: cold sweat, night sweat, hot flashes</p> <p><u>Somatic cluster</u>: pain, stiffness or soreness in joints, neck or shoulder, headache</p> <p><i>Women without metabolic syndrome</i> <u>Mental health/sleep/urinary cluster</u>: depression, anxiety, frequent mood changes, forgetfulness, sleep disturbance, leaking urine</p> <p><u>Vasomotor cluster</u>: cold sweat, night sweat, hot flashes</p> <p><u>Somatic cluster</u>: pain, stiffness or soreness in joints, neck, or shoulder, headache</p> <p>Severity symptom clusters <i>Women with metabolic syndrome</i> <u>Mental health cluster</u>: depression, anxiety, frequent mood changes, forgetfulness, dizzy spells</p> <p><u>Vasomotor cluster</u>: cold sweat, night sweat, hot flashes</p> <p><u>Somatic cluster</u>: pain, stiffness or soreness in joints, neck or shoulder</p> <p><i>Women without metabolic syndrome</i> <u>Mental health/sleep</u>: depression, anxiety, frequent mood changes, forgetfulness, sleep disturbance</p> <p><u>Vasomotor/genital cluster</u>: cold sweat, night sweat, hot flashes, vaginal dryness</p> <p><u>Somatic cluster</u>: pain, stiffness or soreness in joints, neck, or shoulder, headache, dizzy spell</p>	
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EFA	<p>Ng et al., 2020¹⁵</p> <p><u>Purpose(s)</u>: Examine the longitudinal patterns of symptom clusters in patients with ESRD undergoing dialysis</p> <p>Evaluate their impact on health-related QOL and functional status</p> <p><u>Location</u>: Hong Kong</p>	<p><u>Disease or condition</u>: ESRD</p> <p>$n = 271$</p> <p>Mean age 60.0 (± 11.4) years</p> <p>Gender Female 41.7% Male 58.3%</p> <p>Race or ethnicity NR</p> <p>Education NR</p> <p>Employment status</p>	<p><u>Instrument(s)</u>: Dialysis Symptom Index – 30 symptoms Kidney Disease QOL – 36 items</p> <p><u>Symptom dimension(s)</u>: distress</p>	<p>Four symptom clusters were identified across three time points:</p> <p>Enrollment <u>Uremic cluster</u>: lightheadedness or dizziness, numbness or tingling in feet, feeling tired or lack of energy, bone/joint pain, headache, muscle soreness, difficulty concentrating</p> <p><u>Gastrointestinal cluster</u>: nausea, vomiting, diarrhea</p> <p><u>Skin cluster</u>: dry skin, itching, trouble falling asleep, trouble staying asleep</p> <p><u>Emotional cluster</u>: worrying, feeling nervous, feeling irritable, feeling sad, feeling anxious</p>	

		Retired 54.6%		<p>6 months</p> <p><u>Uremic cluster</u>: numbness or tingling in feet, muscle soreness, shortness of breath</p> <p><u>Gastrointestinal cluster</u>: nausea, vomiting, decreased appetite, decreased interest in sex</p> <p><u>Skin cluster</u>: dry skin, itching, trouble falling asleep, trouble staying asleep</p> <p><u>Emotional cluster</u>: worrying, feeling nervous, feeling irritable, feeling sad, feeling anxious, trouble falling asleep, trouble staying asleep</p> <p>12 months</p> <p><u>Uremic cluster</u>: lightheadedness or dizziness, numbness or tingling in feet, feeling tired or lack of energy, difficulty concentrating, shortness of breath, decreased appetite, muscle cramps</p> <p><u>Gastrointestinal cluster</u>: nausea, vomiting</p> <p><u>Skin cluster</u>: dry skin, itching</p> <p><u>Emotional cluster</u>: worrying, feeling nervous, feeling irritable, feeling sad, feeling anxious, headache, muscle soreness</p>	
EFA	<p>Seppala et al., 2020¹⁶</p> <p><u>Purpose(s)</u>: Explore whether identifiable symptom factors exist in a well-documented cohort of IPF patients</p> <p>Explore whether these factors have an impact on QOL</p> <p><u>Location</u>: Finland</p>	<p><u>Disease or condition</u>: IPF</p> <p>$n = 245$</p> <p>Mean age 74 (range 48 to 92) years</p> <p>Gender Female 44% Male 66%</p> <p>Race or ethnicity NR</p> <p>Education Mean 10 (± 4) years</p>	<p><u>Instrument(s)</u>: ESAS – 9 symptoms</p> <p><u>Symptom dimension(s)</u>: severity</p>	<p>Three symptom clusters were identified:</p> <p><u>Emotional cluster</u>: nausea, depression, anxiety, insomnia, loss of appetite</p> <p><u>Pain cluster</u>: pain at rest, pain in movement</p> <p><u>Respiratory symptoms cluster</u>: tiredness, shortness of breath, cough, wellbeing</p>	

		Employment status Working 9%			
EFA	<p>Yang et al., 2020¹⁷</p> <p><u>Purpose(s)</u>: Investigate symptom clusters in patients with acute exacerbation of COPD</p> <p>Explore the symptom clusters' influencing factors and relationships with inflammatory biomarkers</p> <p><u>Location</u>: China</p>	<p><u>Disease or condition</u>: COPD</p> <p>$n = 151$</p> <p>Mean age 67.3 (± 7.4) years</p> <p>Gender Female 15.2% Male 84.8%</p> <p>Race or ethnicity NR</p> <p>Education \leqPrimary school 36.4% Middle school 32.5% \geqHigh school 31.1%</p> <p>Monthly income in RMB <1,000 16.6% ~1,000 31.8% ~2,000 21.2% ~3,000 21.8% >5,000 8.6%</p>	<p><u>Instrument(s)</u>: MSAS revised Chinese version – 19 symptoms</p> <p><u>Symptom dimension(s)</u>: severity</p>	<p>Two symptom clusters were identified:</p> <p><u>Emotional cluster</u>: worrying, feeling sad, feeling nervous, difficulty in concentrating, feeling irritable, "I do not look like myself," difficulty in sleeping</p> <p><u>Respiratory functional cluster</u>: dry mouth, feeling drowsy, cough, lack of energy, shortness of breath</p>	Procalcitonin and C-reactive protein
EFA	<p>Yates et al., 2015¹⁸</p> <p><u>Purpose(s)</u>: Identify and compare symptom clusters in younger (<60 years) and older (≥ 60 years) patients undergoing cancer treatment</p> <p><u>Location</u>: Australia and the United States</p>	<p><u>Disease or condition</u>: cancer</p> <p>Total sample $n = 593$ <60 years $n = 263$ ≥ 60 years $n = 330$</p> <p>Mean age NR</p> <p>Gender Female 54.6% Male 45.4%</p> <p>Race or ethnicity NR</p> <p>Education</p>	<p><u>Instrument(s)</u>: MSAS – 32 items</p> <p><u>Symptom dimension(s)</u>: occurrence</p>	<p>Seven symptom clusters were identified using occurrence for younger and older patients:</p> <p>Younger (<60 years) <u>Treatment-related cluster</u>: dry mouth, difficulty swallowing, shortness of breath, lack of appetite, nausea, vomiting, lack of energy, change in food tastes, feeling dizzy, cough, weight loss, constipation, pain, feeling drowsy, mouth sores, feeling nervous, I do not look like myself, difficulty concentrating, feeling bloated</p> <p><u>Mood/cognitive cluster</u>: worrying, feeling sad, feeling nervous, feeling irritable, difficulty concentrating, lack of energy, difficulty sleeping, problems with sexual interest, I do not look like myself</p>	

		<p>Post high school 61.4%</p> <p>Employment or income NR</p>		<p><u>Malaise cluster</u>: lack of energy, feeling drowsy, lack of appetite, nausea, difficulty concentrating, diarrhea, feeling bloated, feeling nervous, difficulty sleeping</p> <p><u>Treatment-related gastrointestinal cluster</u>: vomiting, nausea, not itching</p> <p><u>Genitourinary cluster</u>: problems with urination, problems with sexual interest</p> <p><u>Hormonal cluster</u>: sweats, difficulty sleeping, pain, not weight loss</p> <p><u>Chemotherapy toxicity cluster</u>: hair loss, change in food tastes, I do not look like myself, mouth sores, constipation, feeling bloated, swelling of arms/legs, dry mouth</p> <p>Older (≥60 years) patients</p> <p><u>Malaise cluster</u>: feeling drowsy, lack of energy, difficulty concentrating, difficulty sleeping, feeling nervous, feeling sad, feeling irritable, feeling dizzy, problems with sexual interest, sweats</p> <p><u>Mood/cognitive cluster</u>: worrying, feeling sad, feeling nervous, feeling irritable, lack of energy, difficulty concentrating, lack of appetite, nausea, feeling drowsy, change in food tastes, constipation, I do not look like myself, feeling bloated, numbness/tingling in hands/feet</p> <p><u>Aerodigestive cluster</u>: shortness of breath, cough, dry mouth, difficulty swallowing, lack of appetite, feeling bloated, feeling nervous, lack of energy, nausea, swelling of arms/legs, feeling dizzy, feeling sad, pain, feeling drowsy, difficulty sleeping</p> <p><u>Genitourinary cluster</u>: problems with urination, diarrhea, problems with sexual interest, feeling irritable</p>	
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Abbreviations: CFA = confirmatory factor analysis; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; EFA = exploratory factor analysis; ESRD = end-stage renal disease; FA = factor analysis; HCA = hierarchical cluster analysis; HF = heart failure; IBS = irritable bowel syndrome; IPF = idiopathic pulmonary fibrosis; MSAS = Memorial Symptom Assessment Scale; NR = not reported; PSQI = Pittsburgh Sleep Quality Index; PTSD = posttraumatic stress disorder; QOL = quality of life; RMB = renminbi; SDS = Symptom Distress Scale; T2DM = type 2 diabetes mellitus

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