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Clinical Characterization and Molecular Mechanisms of Dyspnea in Oncology Outpatients Undergoing Chemotherapy

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Clinical Characterization and Molecular Mechanisms of Dyspnea in Oncology Outpatients Undergoing Chemotherapy

by
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DISSERTATION
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Abstract

Clinical Characterization and Molecular Mechanisms of Dyspnea in Oncology Outpatients Undergoing Chemotherapy

Joosun Shin

Dyspnea is defined as “a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity”. Dyspnea occurs in approximately 10% to 70% of oncology patients. This broad range in its prevalence rates suggests that dyspnea has a large amount of inter-individual variability. In addition, the risk factors for dyspnea in patients with cancer are likely to be multifactorial. This variability makes it difficult to characterize the “dyspnea experience” of oncology patients and determine factors associated with this symptom. Consequently, dyspnea decreases oncology patients’ quality of life and, in some cases, overall survival. Yet, definitive interventions do not exist. Therefore, the aims of this dissertation research were to: 1) develop the Multifactorial Model of Dyspnea in Patients with Cancer; 2) systematically review studies published since 2009 that evaluated for dyspnea in patients with cancer; 3) identify subgroups of patients with distinct shortness of breath profiles in a sample of outpatients receiving chemotherapy and evaluate for differences in a variety of demographic, clinical, and symptom characteristics; and 4) determine the most influential perturbed inflammatory pathways between patients with and without dyspnea.

In terms of Aim 1, a conceptual paper provides an overview of the physiology of normal breathing; the pathophysiology of dyspnea; and factors that contribute to dyspnea in oncology patients. Specific factors that were included in the Multifactorial Model of Dyspnea in Patients with Cancer were: person, clinical, and cancer-related factors, as well as respiratory muscle weakness, co-occurring symptoms, and stress. While this paper provides a summary of the evidence on the mechanisms and factors associated with dyspnea in patients with cancer, the paucity of research on this symptom suggests numerous areas for investigation. This paper

concludes that progress will not be made in the effective management of dyspnea without increased knowledge of its associated risk factors and underlying mechanisms.

In terms of Aim 2, in a systematic review, 117 studies were identified that evaluated for dyspnea in patients with cancer. This systematic review summarized the prevalence, intensity, distress, and impact of dyspnea in oncology patients and identified research gaps. Across these studies, the intensity of dyspnea was the most common symptom dimension that was evaluated followed by impact and distress. Depression and anxiety were the most common symptoms that co-occurred with dyspnea. Future research studies need to use valid and reliable multidimensional measures. In addition, given the paucity of studies on mechanism(s) that underlie dyspnea in patients with cancer, future research is warranted to determine specific biomarkers for dyspnea.

In terms of Aim 3, in outpatients receiving their second or third cycle of chemotherapy, four distinct shortness of breath profiles were identified (None [70.5%]; Decreasing [8.2%]; Increasing [7.8%], High [13.5%]). Findings suggest that risk factors for membership in High class include history of smoking, self-reported diagnosis of lung disease, having lung cancer, and receipt of a higher number of cancer treatments. In terms of symptom dimensions, patients in the High class reported more frequent and severe shortness of breath. In addition, compared to None class, patients in the other three classes reported higher occurrence rates for chest tightness and difficulty breathing. Compared to None class, patients in the Decreasing and High classes reported higher occurrence rates for cough. Regarding the impact of shortness of breath, compared to None class, patients in the High class reported poorer physical, psychological, and social functioning.

In addition, we evaluated associations between shortness of breath and global, cancer-specific, and cumulative life stress, as well as resilience and common co-occurring symptoms. Compared to None class, patients in the Decreasing and High classes had higher global and cancer-specific stress scores. Patients in the High class reported higher occurrence rates for

several adverse childhood experiences. In addition, our findings suggested that compared to None class, patients in the Decreasing and High classes had higher depression, anxiety, and morning fatigue scores and lower morning energy and cognitive function scores.

In terms of Aim 4, given the paucity of research on underlying mechanism(s) for dyspnea in patients with cancer and the potential contribution of inflammatory mechanisms, whole transcriptome gene expression and pathway impact analyses were done to evaluate for associations between this symptom and perturbations in inflammatory pathways. Among 73 significantly perturbed Kyoto Encyclopedia of Genes and Genomes signaling pathways, 29 were related to inflammatory mechanisms. Findings from this study provide preliminary support for the hypothesis that pulmonary and systemic inflammation contribute to the occurrence of dyspnea in patients receiving chemotherapy.

To evaluate the interconnections between and among these inflammatory pathways, an unweighted knowledge network was created using the specific pathway maps. Three centrality measures (i.e., betweenness, closeness, degree) were calculated to gain insights into the structural importance of each node. The mitogen-activated protein kinase (MAPK) signaling pathway node had the highest closeness, betweenness, and degree scores. The next ten pathways with the highest centrality scores were: Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathway; apoptosis, phosphatidylinositol 3-kinase (PI3K)-protein kinase B (Akt) signaling pathway, natural killer (NK)-cell mediated cytotoxicity, neutrophil extracellular trap (NET) formation, nuclear factor kappa light chain enhancer of activated B cells (NF-kappa B) signaling pathway, cytokine-cytokine receptor interaction, nucleotide-binding and oligomerization domain (NOD)-like receptor signaling pathway, Forkhead box O (FoxO) signaling pathway, and chemokine signaling pathway. In addition, five common respiratory disease-related pathways, that may share mechanisms with cancer-related dyspnea, were perturbed. These findings warrant validation. This dissertation concludes with implications for clinical practice and future research.

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List of Abbreviations

AFI = Attentional Function Index

AMPS = Assessment of Motor and Process Skills

ARRB2 = arrestin β-2

ASCO = American Society of Clinical Oncology

ATS = American Thoracic Society

AUDIT = Alcohol Use Disorders Identification Test

BDI = Baseline Dyspnea Index

BIC = Bayesian Information Criterion

BRCA = BReast CAncer

CDRS = Connor-Davidson Resilience Scale

CDS = Cancer Dyspnea Scale

CES-D = Center for Epidemiological Studies-Depression scale (CES-D)

CINAHL = Cumulated Index to Nursing and Allied Health Literature

COPD = Chronic obstructive pulmonary disease

COVID-19 = coronavirus disease 2019

CRQ = Chronic Respiratory Questionnaire

DAMP = Damage-associated Molecular Pattern

DILD = Drug-induced lung disease

DL_{CO} = Diffusing capacity for carbon monoxide

DRG = Dorsal respiratory group

DSM-IV = Diagnostic and Statistical Manual of Mental Disorders

D-12 = Dyspnea-12

EM = Expectation-Maximization

EMT = Epithelial-Mesenchymal Transition

EORTC-QLQ C-30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core-30

ESAS = Edmonton Symptom Assessment System

FACT-L = Functional Assessment of Cancer Therapy-Lung

FDR = false discovery rate

FEV1 = Forced expiratory volume in one second

FoxO = Forkhead box O

GSDS = General Sleep Disturbance Scale

HADS = Hospital Anxiety and Depression Scale

HFrEF = heart failure with reduced ejection fraction

HPA = Hypothalamic-pituitary-adrenal

HTR3B = 3B subtype receptor

HUGO = Human Genome Organization

IL = Interleukin

IES-R = Impact of Event Scale-Revised

IPPA = Individually Prioritized Problem Assessment

JAK-STAT = Janus-Activated Kinase-Signal Transducer and Activator of Transcription

J-receptors = Juxta capillary receptors

KEGG = Kyoto encyclopedia of genes and genomes

KPS = Karnofsky Performance Status

LFS = Lee Fatigue Scale

LCA = Latent Class Analysis

LC-13 = Lung Cancer-13

LCSS = Lung Cancer Symptom Scale

LSC-R = Life Stressor Checklist-Revised

MAPK = mitogen-activated protein kinase

MCID = minimal clinically important difference

MCS = Mental Component Summary

MDASI = MD Anderson Symptom Index

MeSH = medical subject headings

MIP = maximum inspiratory pressure

MRC = Medical Research Council

MSAS = Memorial Symptom Assessment Scale

MQOLS-PV = Multidimensional QOL Scale-Patient Version

NCCN = National Comprehensive Cancer Network

NET = Neutrophil Extracellular Traps

NF-kB = Nuclear Factor kappa-light-chain-enhancer of activated B cells

NHLBI = National Heart, Lung, and Blood Institute's

NK = Natural Killer

NOD = Nucleotide Oligomerization Domain

NRS = Numeric Rating Scale

OCD = Oxygen Cost Diagram

PAMP = Pathogen Associated Molecular Patterns

PCO_2 = Partial pressure of carbon dioxide

PCS = Physical Component Summary

PFTs = pulmonary function tests

PIA = Pathway Impact Analysis

PI3K-AKT = Phosphatidylinositol 3-kinase/Protein Kinase B

PO_2 = Partial pressure of oxygen

pPERT = Combined Perturbation *P*-Value Using Fisher's Method Adjusted Using the Bonferroni Method

PRG = Pontine respiratory group

PRISMA-P = Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

PTSD = post-traumatic stress disorder

PSS = Perceived Stress Scale

QOL = quality of life

RBC = red blood cell

RCTs = Randomized controlled trials

RDOS = respiratory distress observation scale

RNA = ribonucleic acid

ROS = Reactive Oxygen Species

SCQ = Self-Administered Comorbidity Questionnaire

SD = Standard Deviation

SF-12 = Medical Outcomes Study-Short Form

SLEs = Stressful Life Events

SNP = single nucleotide polymorphism

SpO2 = oxygen saturation

SPSS = Statistical Package for the Social Sciences

STAI-S = Spielberger State Anxiety Inventory

STAI-T = Spielberger Trait Anxiety Inventory

UCSD SOBQ = University of California San Diego Shortness of Breath Questionnaire

VRG = Ventral respiratory group

VLRM = Vuong-Lo-Mendell-Rubin Likelihood Ratio Test

5-HT = serotonergic 5-hydroxytryptamine

5-HRRLPR = serotonin-transporter-linked promoter region

6MWT = six-minute walk test

Chapter 1

Introduction to Dissertation

Dyspnea is an extremely distressing and common symptom in patients with cancer. [1] For patients with lung cancer [2-4] or advanced cancer, [5-7] the prevalence rates for dyspnea range from 10% to 90%. While this broad range in prevalence rates suggests that a large amount of inter-individual variability exists, risk factors associated with this variability in dyspnea remain unknown. In addition, because dyspnea is not routinely assessed and documented during a clinical encounter, [8] patients do not receive timely symptom management interventions. [9] As a result, under-controlled and persistent dyspnea has a negative impact on oncology patients' quality of life and, in some cases, is associated with decreases in survival. [10] One way to improve the assessment and development of targeted interventions is to identify risk factors and mechanisms that underlie dyspnea in patients with cancer.

CLINICAL CHARACTERIZATION OF DYSPNEA

The American Thoracic Society defined dyspnea as “a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity” (p 436-437). [11] In addition, the American Thoracic Society noted that “the experience of dyspnea derives from interactions among multiple physiological, psychological, social, and environmental factors, and may induce secondary physiological and behavioral responses” (p 436-437). [11] The risk factors for the occurrence of dyspnea in patients with cancer are likely to be multifactorial. [12-14] Specifically, factors that contribute to this variability in patients with cancer include: gender, cancer types, presence of metastatic disease, receipt of previous cancer treatment(s), smoking history, environmental factors, comorbidities, [1] and/or presence of co-occurring symptoms. [5] However, a comprehensive description of these factors in patients with heterogenous types of cancer undergoing chemotherapy is not available in the extant literature. Therefore, exact prevalence rates and associated risk factors in cancer patients undergoing chemotherapy warrant additional investigation. In addition, despite the growing body of

evidence on the role of stress in oncology patients' symptom experience, no studies were identified that evaluated for associations between shortness of breath and stress. Additional studies are warranted to evaluate the roles of a variety of stress (i.e., global, cancer-specific, and cumulative life stress) and resilience on the patients' experience of dyspnea.

In terms of symptom dimensions, dyspnea is a multidimensional symptom that warrants evaluation using the domains of sensory-perceptual experience (i.e., intensity), affective distress, and impact (i.e., quality of life). [11] While a number of measures are used routinely in dyspnea research (e.g., Medical Research Council Dyspnea scale, [15-18] Modified Borg scale, [19-21] numeric rating scale [22-24]), most of them do not assess the multiple dimensions of patient's experience with dyspnea. [11, 25] In addition, very few measures have included an assessment of the affective dimension of dyspnea. [26-30] Additional studies are warranted to address this lack of knowledge regarding the multiple dimensions of the symptom experience of shortness of breath in patients with cancer.

MECHANISM(S) UNDERLYING DYSPNEA

Limited treatments are available for dyspnea. [25] One of the reasons for this limitation is a lack of understanding of the mechanisms that underlie dyspnea. In terms of molecular mechanisms of dyspnea in patients with cancer, only three candidate gene studies were identified that evaluated for associations between dyspnea and this type of molecular marker. [31-33] In a longitudinal study of lung cancer survivors, [32] the severity of dyspnea was associated with SNPs in IL-6 and IL-1β. In a cross-sectional study of patients with non-small cell lung cancer, [33] three SNPs in the BRCA1 gene were associated with the severity of dyspnea. Finally, in another longitudinal study of patients with advanced cancer, [31] individuals who were homozygous for the rare allele in the 5-hydroxytryptamine (serotonin) receptor 3B gene reported severe dyspnea. While these genetic studies provide some information on the molecular mechanisms of dyspnea, [31-33] several limitations warrant consideration. First, only a limited number of candidate genes were evaluated. These candidate genes were selected based on a

priori knowledge and/or hypotheses regarding their biological and functional impact on the symptom of interest. [34] Given the limited information on the mechanisms that underlie dyspnea in oncology patients, additional types of molecular markers warrant evaluation.

In terms of plausible mechanistic hypotheses, pulmonary [35] and systemic [36] inflammation may contribute to the development of dyspnea in patients receiving chemotherapy. In a review that explained the role of afferent neurons in dyspnea, [37] airway inflammation and associated perturbations in vagal afferent neurons appear to play central roles in the development of dyspnea. Inflammation results in the activation of bronchopulmonary C-fibers that induce dyspnea. [37] This inflammatory process causes the induction of airway wall remodeling that is characterized by smooth muscle proliferation. [35] This remodeling increases tension in airway smooth muscles and contributes to the development of dyspnea. [37]

In addition, tumor cells and cytotoxic drugs may contribute to the development of dyspnea through the stimulation of innate and adaptive immune mechanisms. [38, 39] This systemic response results in the activation of a number of inflammatory signaling pathways; the recruitment of acute and/or chronic inflammatory cells; and the destruction of bronchoalveolar structures. [40-42] Moreover, systemic inflammation may contribute to the development of dyspnea through its effects on skeletal muscle (e.g., diaphragm). [36] In two preclinical studies, [43, 44] systemic administration of a clinical dose of doxorubicin resulted in inflammation and weakness of the diaphragm.

While this body of research is increasing, no studies has evaluated for associations between the occurrence of dyspnea and pathway perturbations in patients undergoing chemotherapy. The potential identification of perturbed inflammatory pathways and their patterns of interactions [45] may increase our understanding of the mechanisms that underlie dyspnea.

FOCUS OF THIS DISSERTATION RESEARCH

Therefore, two aims of this dissertation research were to: 1) create a comprehensive list of risk factors and associated mechanisms based on the newly developed conceptual model (i.e., the Multifactorial Model of Dyspnea in Patients with Cancer) and 2) conduct a systematic review of the literature to evaluate the occurrence of and characteristics associated with dyspnea in oncology patients. Following the development of these two theoretical papers, [46, 47] the remaining aims utilized phenotypic and molecular data from a heterogeneous sample of oncology patients (n=1329) who were followed over two cycles of chemotherapy. The additional study aims were to: 3) identify subgroups of patients with distinct dyspnea profiles, evaluate for differences among these subgroups in demographic and clinical characteristics, evaluate for differences among these subgroups in various dimensions of dyspnea (i.e., severity, frequency, distress,; and evaluate for differences among these subgroups in quality of life (i.e., impacts of dyspnea) outcomes; 4) evaluate for differences among these subgroups in levels of global, cancer-specific, and cumulative life stress and resilience; evaluate for differences in the occurrence rates for various stressful life events, and evaluate for differences in the severity of common symptoms; and 5) evaluate for perturbed inflammatory pathways between patients with and without shortness of breath.

This dissertation consists of five papers. The first paper describes a conceptual framework for dyspnea entitled the Multifactorial Model of Dyspnea in Patients with Cancer. [47] The second paper is a systematic review of dyspnea in patients with cancer. [46] The third paper identifies subgroups of patients with distinct shortness of breath profiles and evaluates for differences in a comprehensive list of demographic and clinical characteristics among these subgroups. The fourth paper, that builds on the third paper, reports on differences in a variety of types of stress (i.e., global, cancer-specific, and cumulative life stress), resilience, and common symptoms among these subgroups. The fifth paper reports on perturbed inflammatory pathways and an associated knowledge network in oncology patients with and without dyspnea.

The first paper (Chapter 2) presents a conceptual framework of dyspnea, entitled the Multifactorial Model of Dyspnea in Patients with Cancer. [47] This conceptual model is an adaption of the Mismatch Theory of Dyspnea [48] that was tailored for patients with cancer. The factors included in this conceptual model are based on a recent systematic review of the literature on dyspnea in oncology patients. [46] The specific factors in the model include: person, clinical, and cancer-related factors, as well as respiratory muscle weakness, co-occurring symptoms, and stress. In this paper, [47] the mechanisms that underlie normal breathing in healthy individuals were summarized, followed by a description of the mechanisms that underlie dyspnea using the Mismatch Theory of Dyspnea. In addition, evidence to support each of the factors that contribute to dyspnea in patients with cancer was summarized and critiqued. This paper concluded with recommendations for clinical practice and research. This chapter is a reprint of the original paper that is in press in the *Oncology Nursing Forum*. [47]

The second paper (Chapter 3) reports on findings from a systematic review of 117 studies, published from 2009 to 2022, that evaluated for dyspnea in patients receiving chemotherapy. The weighted grand mean prevalence of dyspnea in patients with advanced cancer was 58.0%. Across these studies, the most common symptom dimension used to assess dyspnea was intensity (i.e., 110 out of 117 studies (94.0%)), followed by impact in 42 studies (35.9%), occurrence in 37 studies (31.6%), distress in 13 studies (11.1%), and frequency in 4 studies (3.4%). In terms of the domain of sensory-perceptual experience, the Medical Research Council dyspnea scale [49] and the modified Borg scale [50] were the most common measures used to assess intensity. In terms of the domain of affective distress, the Numeric Rating Scale was the most common measure used to assess affective distress associated with dyspnea. In terms of the impact of dyspnea, the most common domains that were assessed included: functional exercise capacity, interference with daily activities, quality of life, and survival. The six-minute walk test was the most common measure that was used to evaluate functional exercise capacity. [51] In terms of co-occurring symptoms, depression and anxiety were the

most common symptoms that co-occurred with dyspnea. In terms of biomarkers associated with dyspnea, pulmonary function tests were the most common ones that were used. This chapter is a reprint of the original paper that was published in the *Critical Review of Oncology and Hematology.* [46]

In the third paper (Chapter 4), we identified subgroups of patients with distinct shortness of breath profiles; evaluated for differences among these subgroups in demographic and clinical characteristics; evaluated for differences among symptom dimensions of shortness of breath, and evaluated for differences in quality-of-life outcomes. Outpatients (n=1338) completed the dyspnea item six times over two chemotherapy cycles. All of the other measures were assessed at enrollment (i.e., prior to the second or third cycle of chemotherapy).

The occurrence of shortness of breath was assessed using the Memorial Symptom Assessment Scale. Latent class analysis was used to identify subgroups of patients with distinct shortness of breath profiles. Four distinct shortness of breath profiles were identified (None [70.5%], Decreasing [8.2%], Increasing [7.8%], High [13.5%]). Risk factors for membership in High class included: history of smoking, self-reported diagnosis of lung disease, having lung cancer, and receipt of a higher number of cancer treatments. In addition, compared to the Decreasing and Increasing classes, the High class's episodes of shortness of breath were more frequent and more severe. Compared to the None class, High class reported poorer physical, psychological, and social functioning. This chapter is a reprint of the original paper that was published in the *Journal of Pain and Symptom Management*. [52]

In the fourth paper (Chapter 5), that builds on the third paper, [52] we evaluated for differences among subgroups in levels of global, cancer-specific, and cumulative life stress, as well as resilience; evaluated for differences in the occurrence rates for various stressful life events, and evaluated for differences in the severity of common co-occurring symptoms. The previously identified shortness of breath classes were used in this analysis (i.e., None (70.5%), Decreasing (8.2%), Increasing (7.8%), and High (13.5%)). Compared to the None class,

Decreasing and High classes had higher global and cancer-specific stress scores. The High class reported higher occurrence rates for several adverse childhood experiences. Compared to the None class, Decreasing and High classes had higher depression, anxiety, and morning fatigue scores and lower morning energy and cognitive function scores. This chapter is under review in the *Seminars in Oncology Nursing.*

The fifth paper (Chapter 6) reports on the findings from a study that evaluated for perturbed inflammatory and respiratory disease-related pathways between oncology patients with and without dyspnea. Prior to their second and third cycle of chemotherapy, 1338 patients reported the occurrence of shortness of breath using the Memorial Symptom Assessment Scale. Latent class analysis was used to identify unobserved subgroups of patients with distinct shortness of breath profiles over the six assessments across two cycles of chemotherapy. Among 1338 patients, 943 patients did not report shortness of breath. Of the remaining 395 patients, three distinct shortness of breath profiles were identified (i.e., Decreasing (8.2%), Increasing (7.8%), and High (13.5%)). [52] In the current analysis, we used an extreme phenotype approach to evaluate for perturbed inflammatory and respiratory disease-related pathways between the None and High classes.

Differential gene expression and pathway impact analyses were performed in patients using microarray (None, n = 233; High, n = 60) and RNA-seq (None, n = 242; High, n = 53) technologies. A total of 4922 and 5130 genes were included in the pathway impact analyses for the microarray and RNA-seq samples, respectively. Using Fisher's Combined Probability method, across the two samples, 73 KEGG signaling pathways were significantly perturbed at an FDR of 0.025. Of these, 29 pathways (7 for signal transduction; 13 for immune system; 2 for signaling molecules and interaction; 3 for transport and catabolism; 3 for cell growth and death; and 1 for cell motility) were related to inflammatory mechanisms.

Then, a knowledge network was used to identify the most influential pathway(s) between and among these perturbed inflammatory pathways and their patterns of interactions. This

knowledge network consisted of 26 nodes (i.e., pathways) with 60 edges (average number of neighbors = 4.62). Three pathways (i.e., viral protein interaction with cytokine and cytokine receptor, peroxisome, hippo signaling pathway) were not included in the final knowledge network due to the lack of the interconnection with the other 26 pathways. Signal transduction pathways grouped together within the knowledge network. Subgroups of other inflammatory pathways were connected through these signal transduction pathways. The MAPK signaling pathway node had the highest closeness (0.610), betweenness (0.261), and degree (0.462) centrality indices. Finally, five pathways related to common respiratory diseases were perturbed, namely: COVID-19, influenza A, tuberculosis, pertussis, and asthma.

Dyspnea is a common and distressing symptom that effects a large number of patients with cancer. [46] Despite its associated burden, dyspnea is underestimated in clinical research and practice. [53] As a result, the paucity of research on dyspnea in oncology patients hampers the development and evaluation of potentially effective treatments. This dissertation research is significant and innovative because it is the first to use a person-centered analytic approach (i.e., latent class analysis) to identify subgroups of oncology patients with distinct shortness of breath profiles and evaluate for differences among these subgroups in a variety of demographic, clinical, and symptom characteristics associated with dyspnea. In addition, this research was the first to investigate molecular mechanisms associated with dyspnea in patients receiving chemotherapy using transcriptomic analysis. Given that this work demonstrated associations between dyspnea and inflammation, these studies will stimulate additional evaluations of molecular targets for the development of interventions to alleviate this distressing symptom.

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Chapter 2

Multifactorial Model of Dyspnea in Patients with Cancer

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ABSTRACT

Problem Identification: Dyspnea is a common and distressing symptom for patients with cancer. Although the risk factors for dyspnea in patients with cancer are likely to be multifactorial, a comprehensive description of these risk factors and associated mechanisms are not available in the extant literature.

Literature Search: A search of all of the relevant databases, including Cochrane Library, PubMed, Embase, Web of Science, and CINAHL, was done from January 2009 to May 2022. Case-control and cohort studies that had either a cross-sectional or longitudinal design, as well as randomized controlled trials, were included in the review. Peer-reviewed, full-text articles in English were included. Nineteen studies reported on risk factors for dyspnea. Findings from these 19 studies are summarized in this article to justify the various components of the multifactorial model of dyspnea.

Data Evaluation: The methodological quality of each of the studies was examined using the National Heart, Lung, and Blood Institute's National Institute of Health Quality Assessment Tool for Observational and Cross-Sectional Studies.

Synthesis: A number of factors can influence the occurrence, severity, and/or distress of dyspnea in patients with cancer. Using the Mismatch Theory of Dyspnea as the central core of this Multifactorial Model of Dyspnea in Patients with Cancer, the factors included in this conceptual model. Person, clinical, and cancer-related factors, as well as respiratory muscle weakness, co-occurring symptoms, and stress, are included in this model.

Implications for Practice or Research: The Multifactorial Model of Dyspnea in Patients with Cancer can be used by clinicians to evaluate for multiple factors that contribute to dyspnea and develop individualized and multilevel interventions for patients experiencing this devastating symptom. In addition, this model can be used by researchers as a conceptual framework to guide future studies of risk factors for and mechanisms that underlie dyspnea.

Keywords: breathlessness; cancer; conceptual model; dyspnea; risk factors

INTRODUCTION

Dyspnea is a common and distressing symptom that occurs in ~58% of patients with cancer. [1] Despite its associated burden, dyspnea is underestimated in clinical practice. [2] The ATS defined dyspnea as “a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity” (p 436-437). [3] In addition, the ATS noted that “the experience of dyspnea derives from interactions among multiple physiological, psychological, social, and environmental factors, and may induce secondary physiological and behavioral responses” (p 436-437). [3] While the risk factors for the occurrence and/or severity of dyspnea in patients with cancer are likely to be multifactorial, [4-6] a comprehensive description of these factors and associated mechanisms are not available in the extant literature.

The most recent review on the mechanisms that underlie dyspnea focused on patients with terminal lung cancer. [7] In this review, the authors suggested that the tumor mass, presence of a malignant pleural effusion, and/or respiratory muscle weakness contributed to a mismatch between afferent (i.e., intended respiratory motor output) and efferent (i.e., ventilatory outputs that were accomplished) signaling. [7] While many clinicians associate the occurrence of dyspnea exclusively with patients with lung cancer or patients at the end of life, findings from epidemiologic studies noted that patients with other types and stages of cancer report dyspnea. [6, 8-12]

While the 2021 NCCN Palliative Care Guideline on Dyspnea summarized a number of clinical trials of various pharmacological and non-pharmacological interventions, [13] they concluded that evidence of the efficacy of these interventions is limited. In addition, the ASCO Guideline on Management of Dyspnea in Advanced Cancer noted that an inadequate understanding of the pathophysiology of dyspnea makes it challenging to develop novel interventions. [14] Therefore, the purpose of this paper is to describe the factors that contribute to the mechanisms that underlie dyspnea in patients with cancer. This paper begins with a

summary of the mechanisms that underlie normal breathing in healthy individuals followed by a description of the mechanisms that underlie dyspnea. In addition, the evidence to support each of the factors that contributes to dyspnea in patients with cancer is summarized and critiqued. The paper concludes with recommendations for clinical practice and research.

PHYSIOLOGY OF NORMAL BREATHING

Respiratory muscles

Respiratory muscles, that are used for inspiration and expiration, include the internal and external intercostal muscles, the diaphragm, and the muscles of the abdomen, neck, and upper limbs. [15] While the diaphragm and intercostal muscles generate intrathoracic pressures, the abdominal muscles coordinate with the diaphragm to compensate for the increased ventilatory drive that is needed during exercise. [16]

Mechanoreceptors

Neural innervation and chest wall receptors

Intercostal muscles are innervated by the intercostal nerves that originate in the thoracic spine. [17] The diaphragm is innervated by the phrenic nerve, that originates in the third to fifth cervical spine. [18] Various types of receptors are involved in breathing. Muscle spindles and Golgi tendon organs in the diaphragm and intercostal muscles detect muscle tension and contraction. [7] While muscle spindles are abundant in intercostal muscles, Golgi tendon organs dominate in the diaphragm. [19] These stretch reflex receptors are innervated by spinal motor neurons that project to the somatosensory cortex. [18]

Lung receptors

The lung contains three main mechanoreceptors that transmit afferent information to the respiratory center in the brain (i.e., slowly adapting pulmonary stretch receptors, irritant receptors, C-fibers). [3] Slowly adapting pulmonary stretch receptors, that lie within the smooth muscles of the trachea and central airways, are activated in response to an increase in lung volume and mediate the termination of inspiration. [3] Irritant receptors are located superficially

within the epithelial cells of the carina and large bronchi. [19] Irritant receptors are stimulated by cigarette smoke [19] and various mediators of inflammation (e.g., histamine, bradykinin, serotonin). [7] In addition, irritant receptors mediate bronchoconstriction, coughing, and mucus secretion. [19] Both of these mechanoreceptors transmit information to the respiratory center through the vagus nerve. [20] C-fibers located in the alveolar walls, lung interstitium, and pulmonary capillaries [3] are sensitized by an increase in interstitial fluid volume and/or pulmonary arterial and capillary pressures. [7] In particular, juxta-capillary receptors (i.e, J-receptors, a type of C-fiber), that are located in the alveolar septa, [7] are activated by pulmonary vascular congestion. [21]

Upper airway receptors

The larynx has three primary receptors (i.e., pressure receptors, irritant (or drive) receptors, flow (or cold) receptors). [19] Irritant receptors rapidly respond to changes in and movement of the laryngeal cartilage. [3] Pressure receptors are sensitive to changes in transmural laryngeal pressure. [19] Temperature changes stimulate flow receptors. [19] In terms of facial receptors, the trigeminal nerves are involved in the sensation of dyspnea. [3] While the exact mechanism(s) that underlie the effects of airflow and temperature changes on dyspnea are not established, cold airflow on the face decreases the sensation of dyspnea. [7]

Chemoreceptors

Central chemoreceptors located within the cerebellum and brainstem (e.g., medulla, pons, midbrain) are activated by hypercapnia. [3] Peripheral arterial chemoreceptors within the carotid body are stimulated by hypercapnia, hypoxia, and acidosis. [3] The carotid body comprises around 15% of the total driving force of the respiratory system. [20] Increased afferent information is transmitted to the respiratory center in the lower brainstem, that directly and indirectly increases respiratory neural output. [7]

Respiratory center and brain regions

The respiratory center, located in the medulla oblongata and pons of the brainstem, generates and maintains the rhythm of respiration. [22] Three major groups of neurons compose the respiratory center. The VRG and the DRG, located in the medulla, control the basic rhythm of respiration. [22] In particular, the DRG initiates inspiration and receives pulmonary afferent input from the vagus nerve. [22] The VRG consists of four groups of neurons, that are involved in inspiration and expiration. [22]

The PRG, located in the pons, includes the apneustic and pneumotaxic centers, that control the pattern and rate of breathing. [22] Afferent information ascends from the lower brainstem and is integrated in the cerebral cortex, where dyspnea is perceived. [7] During this process, the symptoms of anxiety and depression, that effect the limbic system, can alter the severity of and distress from dyspnea. [7] The medullary respiratory center receives descending signals from the cerebral cortex and hypothalamus. [23] The hypothalamus is involved in the modulation of respiration in hypoxic and hypercapnic conditions and under stress. [23] The descending signals from the medullary respiratory center are transmitted to the somatic motor neurons located in the anterior horn of the spinal cord. [18]

Mechanisms of normal breathing

Each rhythmic respiratory cycle begins with inspiration and ends with expiration. The respiratory system consists of three components, namely the central neural respiratory center, the sensory input system, and the muscular effector system. [20] During the first step of respiration, the respiratory neural network (i.e., the DRG) in the lower brainstem generates a motor command that is sent to the respiratory muscles. Once the respiratory muscles receive this signal, they initiate inspiration by contracting the diaphragm and intercostal muscles. This process decreases intrathoracic pressure and increases volumes in the thoracic cavity that allow air to enter the lungs. Expiration occurs passively in response to the elastic recoil of the

lungs and thorax. These rhythmic contractions of the respiratory muscles are controlled and monitored by the respiratory centers within the medulla and the pons.

Motor command corollary discharge

Normal breathing results from well-coordinated interactions between the respiratory muscles and the cerebral cortex. [20] When the respiratory neural network in the lower brainstem generates the motor command, copies of the motor command signal (i.e., motor command corollary discharge) are simultaneously transmitted to the cerebral cortex through the limbic system. [7] As a result, the cerebral cortex, a higher brain center, can detect a quantitative and phasic mismatch between afferent and efferent signaling and make adjustments for any disparities. [7]

Respiratory homeostasis

Chemoreceptors and mechanoreceptors are involved in the respiratory feedback loop that sends sensory afferent information to the cerebral cortex through the limbic system. [18] In particular, mechanoreceptors in the lungs, chest wall, airways, and spindles of the respiratory muscles monitor the actual ventilatory motor output. [18] This information is transmitted to the cerebral cortex through the lower brainstem and limbic system. [7] Finally, the cerebral cortex compares the integrated chemical and mechanical sensations with the motor command corollary discharges. [24] Within the normal threshold, the sensory cortex eliminates, minimizes, and/or compensates for the differences between afferent and efferent signals to maintain respiratory homeostasis. [24] As a result, breathing under normal conditions is an unconscious process.

PATHOPHYSIOLOGY OF DYSPNEA

Integrated mismatch theory of dyspnea

Sensory-perceptual/quality components

According to the integrated Mismatch Theory of Dyspnea, [7] when the threshold between motor command corollary discharge and afferent inputs is exceeded, the cerebral

cortex perceives dyspnea (Figure 1). Increased afferent input from mechanoreceptors and chemoreceptors augments the neural input to the respiratory muscles. This enhanced motor command increases the level of ventilation and facilitates gas exchange. Chemoreceptors are stimulated by hypercapnia, hypoxia, and acidosis. [3] Mechanoreceptors are stimulated by increased load and capacity imbalance. For example, increased respiratory load (or pressure) can occur due to lung stiffness, chest wall stiffness, airway flow resistance, and/or an augmented ventilatory demand. On the other hand, reduced capacity of the respiratory muscles results from muscle weakness and hyperinflation. [25] Under these pathological conditions, augmentation of the respiratory drive cannot occur. An increase in ventilatory load and/or a reduction in muscle capacity results in the progressive and continuous mismatch between motor command corollary discharge and integrated afferent information. [7]

Distress components

Anxiety, depression, and anticipatory fear can amplify dyspnea [7, 26] by decreasing the threshold and increasing the sensitivity for dyspnea perception. [7] An unpleasant emotional state is associated with neural activation of the limbic system (e.g., amygdala and anterior insula). [26] Information from the limbic system is integrated into the cerebral cortex and influences the level of dyspnea [7] by affecting higher order neural processing of respiratory sensations. [27] Interestingly, anxiety affects the later higher-order neural processing of respiratory sensations instead of the first-order sensory processing. [27] This finding suggests that the distress component of dyspnea may have distinct mechanisms from the sensory/perceptual component. On the other hand, the mechanisms that underlie dyspnea under negative emotional states may be associated with an excessive ventilatory drive or a blunted perception of achieved ventilatory output. This hypothesis is supported by the finding that individuals prone to panic disorders tended to experience dyspnea even in the absence of decreased ventilatory capacity. [3]

METHODS

In order to develop this model, a systematic review of the prevalence of and risk factors for dyspnea was performed. [1] In brief, in collaboration with a medical librarian, literature search strategies were developed using MeSH terms and various text words related to dyspnea (i.e., breathlessness, shortness of breath, labored breathing, difficulty breathing) in adult oncology patients. The following databases were searched: Cochrane Library, PubMed, Embase, Web of Science, and Cumulative Index to Nursing and Allied Health Literature. Case-control and cohort studies that had either a cross-sectional or longitudinal design, as well as RCTs were included in the review. Peer-reviewed, full-text articles in English were included. Among the one hundred seventeen studies that met pre-specified inclusion criteria for this systematic review, [1] only nineteen studies reported on risk factors for dyspnea. [5, 6, 8, 28-43] Findings from these nineteen studies are summarized below to justify the various components of the multifactorial model of dyspnea.

FACTORS ASSOCIATED WITH DYSPNEA IN PATIENTS WITH CANCER

As illustrated in Figure 2, a number of factors can influence the occurrence, severity, and/or distress of dyspnea in patients with cancer. Using the Mismatch Theory of Dyspnea [7] as the central core of this Multifactorial Model of Dyspnea in Patients with Cancer, the factors included in this conceptual model are based on a systematic review of the literature. [1] Person, clinical, and cancer-related factors, as well as respiratory muscle weakness, co-occurring symptoms, and stress are included in this model. Select research findings that provide the empiric support for the inclusion of these factors in this model are summarized below.

Person Factors

Age

Older patients with cancer are more likely to report higher dyspnea severity scores. [34, 41] Vertebral deformities, increased chest wall stiffness, and reductions in lung elasticity increase both pressure on respiratory muscles and afferent inputs from pulmonary stretch

receptors. [25] In addition, the aging process contributes to a decrease in the number and size of muscle fibers and a reduction in respiratory muscle strength. [44] A decrease in the capacity of respiratory muscles and an increase in respiratory resistance increase the afferent signals from respiratory muscle spindles. Equally important, as part of the aging process, the amount of alveolar dead space increases, [45] which results in hypoxia and hypercapnia and increases in afferent inputs from chemoreceptors. [46] This continuous mismatch between afferent information and motor command corollary discharge augments neural respiratory drive and increases dyspnea. [7] For these reasons, older patients receiving cancer treatments may be more susceptible to dyspnea. [28, 38, 47, 48]

Sex

Findings regarding sex differences in dyspnea in patients with cancer are inconsistent. While in three studies, [30, 34, 38] male patients were more likely to experience severe dyspnea, in one study, [31] females reported a higher symptom burden. One potential explanation for the higher rates of dyspnea in men is that they have higher rates of smoking [49]. Smokers tend to have higher airway resistance, lower peak oxygen uptake, and lower ventilation output, which increase total breathing efforts. [50] Another plausible hypothesis is that the loss of skeletal muscle mass during chemotherapy differs by sex. As noted in one meta-analysis, [51] skeletal muscle loss was approximately 1.6 times higher in males during chemotherapy. Given that respiratory muscles are skeletal muscles, this loss may contribute to a decrease in respiratory muscle strength and result in the mismatch between the motor command corollary discharge and afferent information.

Socioeconomic status

Across several studies, [29, 34, 38, 41, 42] cancer patients with a lower socioeconomic status reported more severe dyspnea. However, associations between socioeconomic status and dyspnea cannot be fully explained using the Mismatch Theory of Dyspnea. [7] Instead, this finding may reflect health disparities associated with various demographic (e.g., less education,

employment status), clinical (e.g., lower rates of cancer screening, less access to healthcare), social (increased in early childhood adversity), and environmental (e.g., poor neighborhoods, air pollutants, occupational hazards) factors that inter-relate with lower socioeconomic status. [52]

Clinical Factors

Smoking

Previous or current smoking history in patients with cancer was associated with higher occurrence rates [5, 42] and more severe levels of dyspnea. [29] Cigarette smoking is one of the most significant factors for the development of dyspnea in adults. [53-55] For example, not only do persons who smoke have three times higher odds of developing dyspnea than those who do not smoke, [54] they experience dyspnea in the absence of clinical manifestations of chronic airway disease. [50] The underlying mechanisms for dyspnea may include: destruction of small airways, loss of elastic recoil of the lung, lung hyperinflation, and gas trapping due to chronic inflammation. [50, 56] These pathological changes increase the inspiratory resistive work and augment the inspiratory neural drive to the diaphragm. In addition, chronic immune responses change the diaphragm's mechanical properties, [50] which leads to reductions in the voluntary contribution of the diaphragm to overall pressure generation at vital capacity in the lung. [50] As a result, the mismatch between the augmented afferent signaling and ventilatory outputs results in dyspnea in persons with a smoking history.

Respiratory disease

The co-occurrence of respiratory disease contributes to the occurrence and severity of dyspnea in patients with cancer. [6, 29, 32] While COPD is often underdiagnosed in patients with cancer, [57] advanced cancer patients with COPD reported more severe dyspnea. [41] The pathophysiology of COPD is characterized by airflow limitations and loss of elastic recoil, that increase respiratory resistance and augment afferent signals from respiratory muscle spindles. [7] In addition, a rise in PCO_2 increases afferent signals from peripheral chemoreceptors and augments the integrated chemical respiratory sensation. [7] However, respiratory muscle

weakness, common in patients with advanced cancer and COPD, [58, 59] may prevent the conversion of respiratory motor neural output to ventilation that would correspond with an increase in the motor command signal. This mismatch between motor command corollary discharge and integrated afferent information increases the perception of dyspnea. [7]

Heart disease

Presence of congestive heart failure is associated with more severe dyspnea in patients with cancer. [28] Patients with congestive heart failure tend to have reduced lung compliance due to pulmonary edema. [60] These restrictive ventilatory effects magnify the mechanical effort of ventilation. [7] In addition, interstitial tissue edema activates J-receptors, [7] amplifies afferent signals, and increases motor commands and ventilation. [60] Furthermore, cardio-pulmonary interactions in patients with chronic heart disease contribute to the development and maintenance of dyspnea. [60] The lungs of patients with heart failure undergo a progressive remodeling process in the alveolar-capillary membrane that may result in lung fibrosis. [60] This process increases respiratory resistance and creates imbalances in gas exchange, [60] Chronic heart failure worsens the deoxygenation of respiratory muscles and decreases inspiratory muscle strength. [61] This respiratory muscle weakness prevents the fulfillment of ventilatory requirements and maintains dyspnea. [7]

Cancer-Related Factors

Primary or metastatic lung cancer

While the occurrence and severity of dyspnea may vary widely depending on the tumor's location, size, and histology, the presence of advanced lung cancer [29, 31, 32, 34, 41, 47] is associated with severe dyspnea. In patients with primary lung cancer or lung metastases, the tumor can activate single or multiple receptors, [7] namely pulmonary stretch receptors, irritant receptors, and/or pulmonary C fibers (i.e., J-receptors), [18] and augment respiratory neural drive. [7] In addition, lung lesions can hamper gas exchange, which increases arterial PCO_2 and decreases PO_2. This disturbance in gas exchange leads to increases in afferent discharges from

peripheral chemoreceptors and central respiratory drive. [7] However, tumors restrict lung expansion and increase afferent inputs from mechanoreceptors. [7] The increased mismatch between motor command corollary discharge and integrated mechano-chemical respiratory sensations augments dyspnea perception. [7]

Malignant pleural effusion

Dyspnea is a common symptom in the 15% of patients with a malignant pleural effusion. [32] Pleural effusions reduce the efficiency of chest wall expansion and decrease total lung capacity [7] This restrictive ventilatory effect increases sensory information from mechanoreceptors, which augments the motor command, inducing dyspnea. [7] Of note, a large amount of inter-individual variability exists in the effects of malignant pleural effusions on the elasticity and resistance of the lung and chest wall [62] and may differ based on the volume of pleural fluid. [63]

Hepatomegaly and malignant ascites

Patients with liver metastases are more likely to report dyspnea because of hepatomegaly [10] and/or malignant ascites. [10] Enlarged liver and/or ascites elevate the diaphragm, decrease lung volumes, and hamper thoracic expansion. [64] These pressures and restrictions stimulate pulmonary stretch receptors and increase afferent inputs to the cerebral cortex. While the mismatch between motor command corollary discharge and sensory information increases neural ventilatory drive, [7] enlarged liver and/or ascites hamper the diaphragm from accomplishing the ventilatory outputs intended. As a result, the disassociation between afferent and efferent signaling increases a sense of respiratory effort and causes hyperventilation.

Cancer Treatments

Thoracic surgery

Thoracic surgery is associated with dyspnea in patients with lung cancer. [28] In three longitudinal studies that evaluated trajectories of dyspnea, [65-67] dyspnea worsened following

surgery and persisted for 24 months. [68] Dyspnea occurs due to an increase in respiratory muscle work that is required to maintain a normal workload from local damage or lung resection. [28] In addition, thoracic surgery changes the biophysical and biochemical characteristics of pulmonary surfactants that facilitate alveolar expansion on inspiration and prevent alveolar collapse at the end of expiration, [69, 70] In several longitudinal studies, [71-73] a significant increase in respiratory resistance and gas exchange imbalance were found after thoracic surgery. Taken together, these changes increase the load on the respiratory muscles and augment afferent information from mechano-chemo receptors, which amplifies the motor command and induces dyspnea.

Thoracic radiotherapy

Worsening dyspnea following radiotherapy [32, 38, 48] may be the sentinel symptom that represents the development of radiation-induced lung injury. [74] Factors associated with higher levels of dyspnea in patients undergoing radiation included: older age, [48] the total lung radiation dose, [75, 76] heart volume, [76] and the presence of cardiopulmonary comorbidities. [76, 77] In addition, postoperative radiotherapy is associated with a decreased capacity for gas exchange. [78] A higher total dose of radiation was associated with an increase in airway flow resistance at 12 months. [75] This finding suggests that thoracic radiotherapy causes progressive lung damage, inducing scar tissue. [74, 79] These changes result in insufficient ventilation and gas exchange, as well as increased respiratory efforts to expand the stiffened lung, which increase motor command and augments dyspnea.

Drug-induced lung disease

Certain chemotherapeutic agents (i.e., bleomycin, taxanes, methotrexate, platins, gemcitabine), targeted therapies (i.e., tyrosine kinase inhibitors), and immunotherapies can result in DILD (i.e., interstitial pneumonitis, pulmonary fibrosis) and associated dyspnea [80]. As shown in four longitudinal studies, [81-84] chemotherapy induced unexpected lung tissue injuries [85] and deterioration in pulmonary function. [82] Multiple factors may contribute to the

development of drug induced pulmonary toxicities including: older age, male gender, pre-existing lung disease, higher cumulative dose, and previous or concurrent radiotherapy. [81, 82, 84] Decreased lung compliance due to DILD prevents sufficient lung expansion and ventilatory output. An increase in ventilatory efforts to expand the stiffened lung increases the tension of the intercostal muscles and afferent discharges from muscle spindles during inspiration. This discordance between motor command corollary discharge and integrated mechanical respiratory sensation may result in dyspnea. [7]

DILD is characterized by an increase in diffusion distance. [86] This injury occurs as a result of progressive damage in the pulmonary capillary bed, that causes a reduction in the diffusion area. [87] As a result, decreases in arterial PO_2 increase the afferent discharges from peripheral chemoreceptors and integrated chemical respiratory sensations, which may magnify the motor command and increase dyspnea. [7] However, in two studies, [84, 88] while pulmonary toxicity was identified using objective measures, patients did not report increases in dyspnea severity.

Anemia

Anemia occurs in 30% to 90% of patients with cancer and is characterized by a reduction in hemoglobin and hypoxemia. [89] A decrease in oxygen content in peripheral blood activates chemoreceptors. These augmented afferent signals from chemoreceptors are transmitted to the respiratory center in the brain and increase ventilatory drive. [7] Increased ventilatory requirements augment the work of breathing and induce dyspnea. [7]

Respiratory muscle weakness

Respiratory muscle weakness associated with malnutrition, cachexia, and generalized weakness, [90] as well as physical inactivity, [91] contribute to the occurrence and severity of dyspnea. For example, in one cross-sectional study of patients with advanced cancer, [92] the strength of inspiratory muscles was negatively correlated with the intensity of dyspnea.

Cachexia and malnutrition

Cachexia is reported in 50% to 80% of patients with advanced cancer. [93] In particular, cytotoxic chemotherapy and targeted therapy accelerate the loss of skeletal muscle mass, [51, 94] inducing muscle atrophy and muscle weakness. [95] In addition, malnutrition decreases respiratory muscle strength and maximal voluntary ventilation. [90] The reduced capacity of the respiratory muscles and augmented neural ventilatory drive increase the mismatch between the motor command corollary discharge and afferent inputs, inducing dyspnea. [25] Furthermore, respiratory muscle weakness reduces the lung's ability to transfer gas from the alveoli to the blood, [78] that exaggerates chemoreflex responses, increasing the perception of dyspnea. [7]

Physical Inactivity

An increase in dyspnea occurrence [42] and intensity [29, 35] is associated with physical inactivity in oncology patients. One possible explanation for this finding is that cancer and its treatments contribute to a vicious cycle of physical deconditioning, physical inactivity, and respiratory muscle weakness, [96] which increases the ventilatory neural drive and worsens dyspnea. For example, among recipients of allogeneic hematopoietic stem cell transplantation, a two week-isolation during engraftment limited patients' physical activity and resulted in impairments in skeletal muscle oxygenation that was associated with muscle weakness and worsening dyspnea during daily activities. [97] While future studies are warranted to examine the direct role of physical inactivity in respiratory muscle weakness and dyspnea severity, in one cross-sectional study of sedentary community-dwelling older adults, [98] physical inactivity was associated with respiratory weakness, which reduced ventilatory capacity and increased dyspnea.

Co-Occurring Symptoms

Anxiety and depression

Anxiety and depression increase dyspnea intensity in patients with cancer. [8, 29, 41, 99, 100] Some evidence suggests that dyspnea catastrophizing in patients with anxiety and

depression may increase their emotional responses to respiratory sensations. [101] This over-perception of breathing causes higher activation of the limbic systems and increases the neural ventilatory drive, with a resultant worsening of dyspnea. [7, 102] In addition, a higher symptom burden and decreased physical conditioning in patients with anxiety and/or depression appear to play a role in increasing dyspnea. [102, 103]

Fatigue

Fatigue is another symptom that demonstrated a positive relationship with dyspnea. [8, 11, 33, 104-107] For example, in patients with advanced cancer without lung involvement, [88, 108] fatigue was described as a plausible cause for their dyspnea. While the mechanisms that underlie the association between fatigue and dyspnea are not well understood, several hypotheses exist. First, cancer and cancer treatment increase serotonin levels in the central nervous system that leads to the upregulation of serotonergic receptors. [109] These changes reduce somatic motor drive, which contributes to an increase in a sense of effort in respiratory muscles. [109] The second hypothesis is that chemotherapy, directly and indirectly, causes damage to skeletal muscles and skeletal muscle weakness, [88] impairing lung expansion and inhibiting slowly adapting pulmonary stretch receptors. [7] Dyspnea in cancer patients with fatigue may be due to an increase in the mismatch between motor command corollary discharge and integrated mechanical respiratory sensation. [7] Another potential mechanism for the co-occurrence of fatigue and dyspnea is through the activation of vagal afferents associated with cancer and its treatment. [109] These activated vagal afferent send signals to the lungs that induce bronchoconstriction and mucus secretion. These effects increase ventilatory neural drive and augment dyspnea. [110]

Cough

Cough was another symptom that was associated with [111, 112] and clustered with dyspnea in patients with cancer. [113] One hypothesis for this association is that activation of bronchopulmonary C-fibers receptors results in the occurrence of both symptoms. [114]

Stress

Stress, resilience, and coping

While not studied in oncology patients, in a study of the general population, [115] exposure to a higher number of traumatic events and the occurrence of PTSD were associated with increases in airflow limitation. In addition, activation of the HPA axis activation, in response to stress, can increase inspiratory drive by transmitting descending signals to the medullary respiratory center. [23, 116] However, the relationship between dyspnea and HPA axis activation appears to be bi-directional. For example, episodic, excessive, or chronic dyspnea can act as a stressor and activate the HPA axis. [117] In contrast, in a study of patients with chronic dyspnea, [118] moderate to severe dyspnea was associated with higher levels of perceived stress and flatter diurnal cortisol slopes. Given that oncology patients experience a wide variety of stressors, [119] an evaluation of the relationships between dyspnea and stress is warranted.

The use of various coping strategies appears to influence an individual's level of resilience in response to stress. [120] While not completely understood some coping strategies may buffer HPA axis activation and cortico-limbic interactions in response to stress. [120, 121] While no studies have examined associations between dyspnea, stress, resilience, and the use of engagement and disengagement coping strategies, higher levels of dyspnea in patients with COPD were associated lower levels of resilience. [122] Associations between dyspnea, resilience, and coping warrant evaluation in patients with cancer.

IMPLICATIONS FOR FUTURE RESEARCH

While this paper provides a summary of the evidence on the mechanisms and factors associated with dyspnea in patients with cancer, the large amount of inter-individual variability in this symptom across heterogeneous types of cancer and the paucity of research on this symptom suggests numerous areas for investigation. Progress will not be made in the effective management of this symptom without increased knowledge of its underlying mechanisms and associated risk factors. Several areas for future research based on each of the factors in the

conceptual model are summarized in Table 1. While this list of potential research topics is not all inclusive, it may stimulate research on this common symptom that has significant negative effects on all aspects of oncology patients' lives.

IMPLICATIONS FOR CLINICAL PRACTICE

As noted in the Introduction, this paper provides an overview of normal breathing; the pathophysiology of dyspnea; and factors that contribute to dyspnea in oncology patients. While the fundamental mechanisms that underlie this symptom are not well understood, clinicians can use the information on various risk factors to guide their assessments and management of oncology patients. First and foremost, regardless of the type of cancer, clinicians need to perform a comprehensive assessment of dyspnea that includes an evaluation of its severity, distress, and impact. In addition, they need to assess for common co-occurring symptoms. This type of assessment will guide the prescription of appropriate interventions.

For example, if the patient currently smokes, clinicians need to provide education about smoking cessation programs. For patients with co-occurring pulmonary and/or heart diseases, oncology clinicians need to work with patients' primary care physicians to optimize the management of these comorbidities. In addition, patients with dyspnea may benefit from pulmonary rehabilitation programs [14] and psychological interventions (e.g., psychoeducation, stress management, relaxation therapy). [13] In addition, oncology clinicians can recommend nonpharmacologic interventions (e.g., fan therapy, breathing techniques, supplemental oxygen therapy) to improve dyspnea. [13, 14] If patients require pharmacological interventions, opioids can be used to treat acute dyspnea; bronchodilators may be indicated for bronchospasm; and/or corticosteroids to decrease inflammation. [13, 14, 123] Management of psychological distress is a crucial component of effective management of dyspnea. If patients have moderate to severe anxiety and/or depression, the prescription of anxiolytics [13, 14] or antidepressants [124] may decrease dyspnea. Once these interventions are initiated, ongoing assessments are warranted

to evaluate their efficacy and to make adjustments as warranted to optimize the management of dyspnea.

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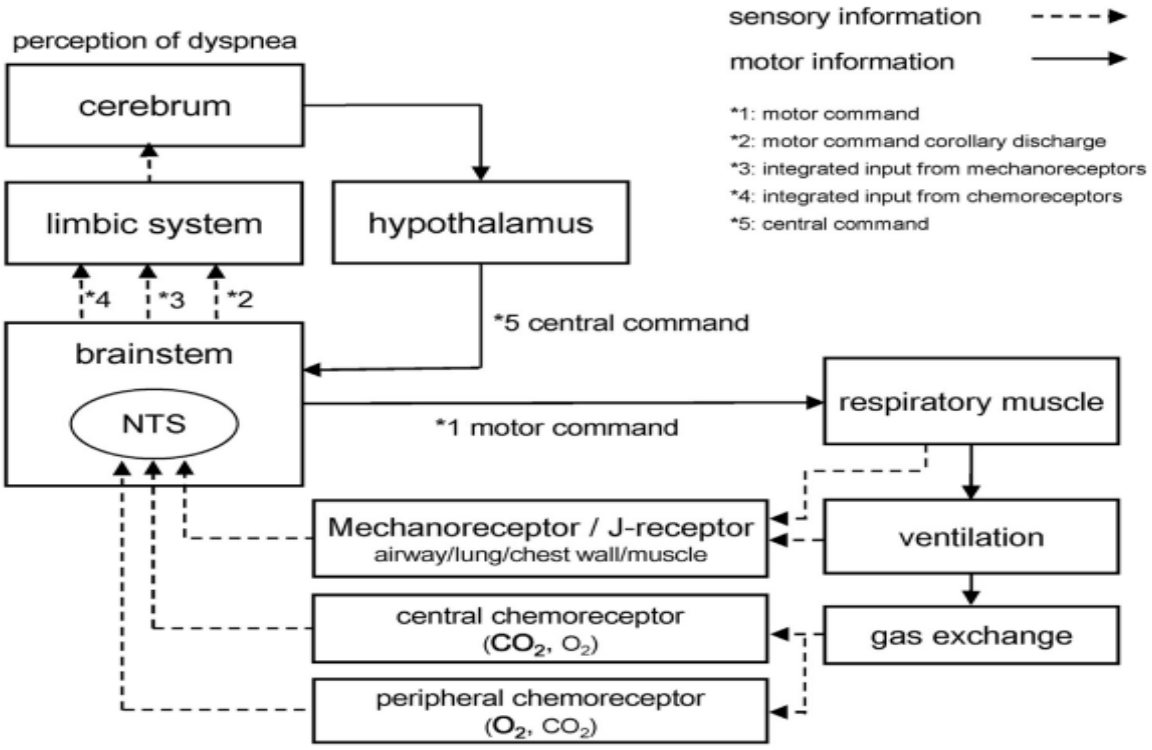

Figure 2.1. Dyspnea pathways. The lower brainstem respiratory neural network produces a motor command (*1) that modulates upper airway patency and drives the respiratory pump muscle. Copies of the motor command signal are transmitted to the limbic system and cerebrum as a type of sensation that reflects the amount of respiratory effort [motor command corollary discharge (*2)]. The ventilatory output, realized by the motor command, is monitored by respiratory mechanoreceptors in the lungs, airways, and muscle spindles in the intercostal muscles. The information is projected to the lower brainstem, limbic system, and cerebral cortex and processed as an integrated mechanical respiratory sensation (*3). The integrated mechanical respiratory sensation and motor command corollary discharge are counter compared in higher brain centers, and the quantitative and/or phasic mismatch causes dyspneic sensation. Further, signals from peripheral and central chemoreceptors are summated as integrated chemical respiratory sensation (*4) in higher brain centers. The integrated chemical respiratory sensation modifies respiratory sensation. The threshold and sensitivity for the perception of dyspnea are also influenced by the mental state. Dyspnea perception augments the central command (*5) that descends as a respiratory drive signal from the hypothalamus to the lower brainstem, which heightens respiratory lower brainstem neural output. The brain respiratory feedback system maintains ventilation at an appropriate level. NTS = nucleus tractus solitarius. Adapted from Fukushi et al.[1] with permission.

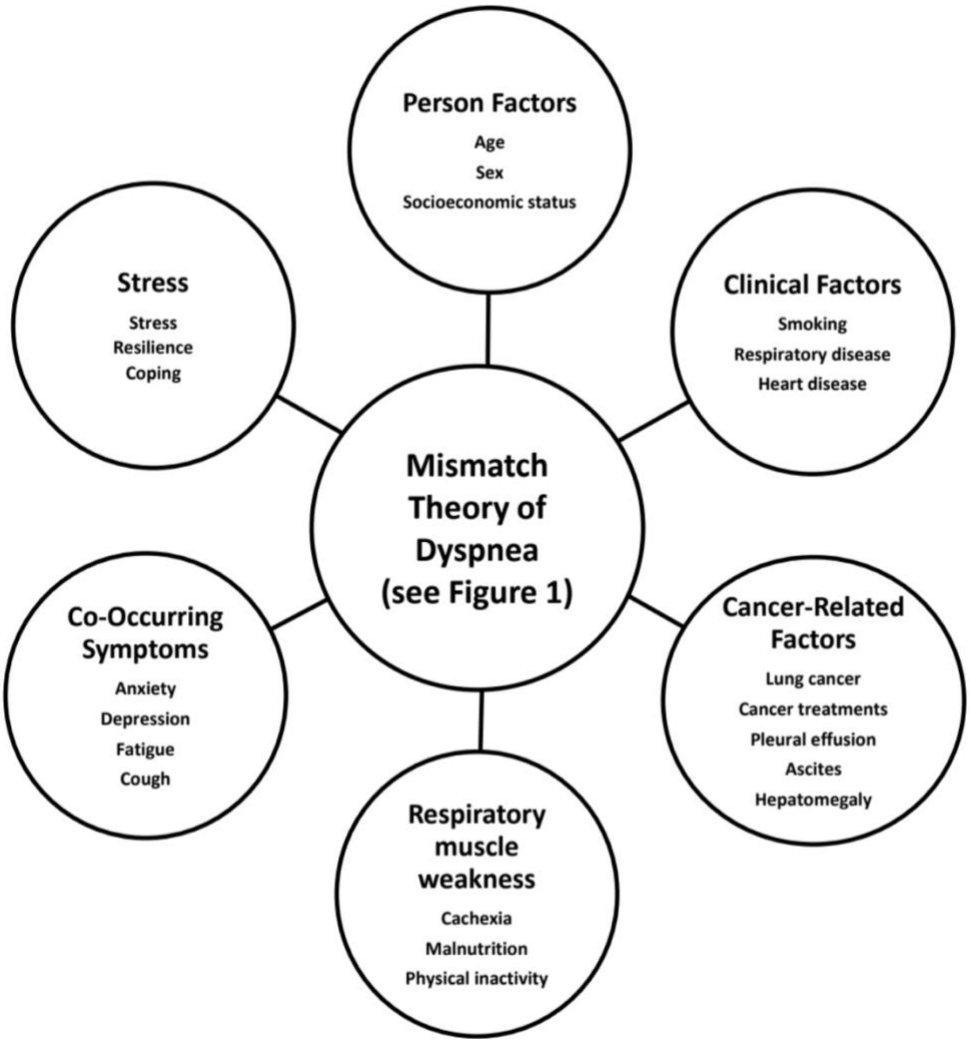

Figure 2.2. The Multifactorial Model of Dyspnea in Patients with Cancer. The model is composed of one big circle that includes the Mismatch Theory of Dyspnea and five small circles that contain factors that are known or hypothesized to be associated with dyspnea. The Multifactorial Model of Dyspnea in Patients with Cancer uses the Mismatch Theory of Dyspnea as its central core. The factors included Person, clinical, and cancer-related factors, respiratory muscle weakness, as well as co-occurring symptoms and stress.

Table 2.1. Recommendations for Future Research on Dyspnea in Patients with Cancer

Topics	Recommendations
Pathophysiologic Mechanisms	Systemic inflammation • Determine the relationships between the occurrence and severity of dyspnea and blood-based markers of inflammation (e.g., serum markers, genotype, gene expression, DNA methylation) Peripheral lung inflammation • Evaluate the relationship between the occurrence and severity of dyspnea and healthy and cancerous lung tissue markers of inflammation (e.g., genotype, gene expression, DNA methylation) Comparison studies • Compare the findings from the blood-based and lung tissue markers of inflammation
Distress-related mechanism	• Determine the relationship between the affective dimension of dyspnea and blood-based markers of inflammation • Utilize functional magnetic imagery to evaluate changes in brain activity associated with the distress dimension of dyspnea
Person Factors	
Age	• Evaluate for age differences in the occurrence, severity, and distress of dyspnea using measures of chronological and biological aging
Sex	• Determine sex differences in the occurrence, severity, and distress of dyspnea • Identify the relative contribution of sex steroid hormones to the occurrence, severity, and distress of dyspnea
Socioeconomic status	• Determine the impact of a variety of social determinants of health on the occurrence, severity, and distress of dyspnea • Examine the relationships between financial toxicity and the occurrence, severity, and distress of dyspnea • Examine the relationships between the occurrence of adverse childhood experiences and the occurrence, severity, and distress of dyspnea in adulthood • Examine the relationship between air pollution and the occurrence and severity of dyspnea • Evaluate the mechanisms by which various social determinants of health influence the occurrence, severity, and distress of dyspnea
Clinical Factors	
Smoking	• Identify lung tissue- and blood-based markers of inflammation associated with dyspnea in smokers with cancer
Respiratory disease	• Evaluate the impact of co-occurring respiratory disease on the occurrence, severity, and distress of dyspnea • Evaluate the differences in inflammatory markers between cancer patients with and without co-occurring respiratory disease • Evaluate for changes in inflammatory markers between cancer patients with and without co-occurring respiratory disease during cancer treatments

Table 2.1. Recommendations for Future Research on Dyspnea in Patients with Cancer

Topics	Recommendations
Heart disease	• Evaluate the impact of co-occurring heart disease on the occurrence, severity, and distress of dyspnea • Evaluate the differences in inflammatory markers between cancer patients with and without co-occurring heart disease • Evaluate for changes in inflammatory markers between cancer patients with and without co-occurring heart disease during cancer treatments
Cancer-Related Factors	
Primary or metastatic lung cancer	• Compare the occurrence, severity, and distress of dyspnea in patients with and without lung cancer • Compare the occurrence, severity, and distress of dyspnea in patients with and without pulmonary metastasis
Malignant pleural effusion	• Compare the occurrence, severity, and distress of dyspnea in patients with and without a malignant pleural effusion
Hepatomegaly and malignant ascites	• Compare the occurrence, severity, and distress of dyspnea in patients with and without hepatomegaly • Compare the occurrence, severity, and distress of dyspnea in patients with and without a malignant ascites
Cancer Treatments	
Thoracic surgery	• Evaluate for changes in the occurrence, severity, and distress of dyspnea in patients following thoracic surgery
Thoracic radiotherapy	• Evaluate for changes in the occurrence, severity, and distress of dyspnea in patients during and following thoracic radiotherapy
Drug-induced lung disease	• Evaluate for changes in the occurrence, severity, and distress of dyspnea in patients during and following chemotherapy • Evaluate for changes in the occurrence, severity, and distress of dyspnea in patients during and following targeted therapy
Anemia	• Evaluate the relationship between the occurrence, severity, and distress of dyspnea and hypoxemia • Evaluate the relationship between the occurrence, severity, and distress of dyspnea and anemia
Respiratory muscle weakness	
Cachexia and malnutrition	• Determine the relationship between cachexia and respiratory muscle weakness in patients with cancer • Determine the relationship between malnutrition and respiratory muscle weakness in patients with cancer • Evaluate the relationships between the occurrence, severity, and distress of dyspnea and cachexia • Evaluate the relationships between the occurrence, severity, and distress of dyspnea and malnutrition
Physical inactivity	• Evaluate the relationships the occurrence, severity, and distress of dyspnea and physical inactivity • Evaluate the relationships between the occurrence, severity, and distress of dyspnea and exercise training • Evaluate the relationships changes in the strength of respiratory muscles following exercise training and biomarkers of inflammation

Table 2.1. Recommendations for Future Research on Dyspnea in Patients with Cancer

Topics	Recommendations
Co-occurring symptoms	
Anxiety and depression	• Determine the relationship between the occurrence, severity, and distress of dyspnea and the co-occurrence of anxiety and dyspnea • Determine the impact of dyspnea in patients with anxiety and/or depression • Evaluate for common and distinct biomarkers associated with the co-occurrence of dyspnea, anxiety, and depression
Fatigue	• Determine the differences between physical fatigue, muscle fatigue, and dyspnea (i.e., sense of effort) • Determine the relationship between the occurrence, severity, and distress of dyspnea and the co-occurrence of fatigue • Evaluate for common and distinct biomarkers associated with the co-occurrence of dyspnea and fatigue
Cough	• Determine the relationship between the occurrence, severity, and distress of dyspnea and the co-occurrence of cough • Evaluate for common and distinct biomarkers associated with the co-occurrence of dyspnea and cough
Stress	
Stress	• Determine the relationship between the occurrence, severity, and distress of dyspnea and various types of stress (e.g., global, cancer-specific, cumulative life stress) • Determine impact of dyspnea in patients with higher stress levels • Evaluate for neuro-endocrine and immune mechanisms that underlie the relationship between stress and dyspnea
Resilience	• Determine the relationship between the occurrence, severity, and distress of dyspnea and resilience • Evaluate the relationship between levels of resilience and the impact of dyspnea on patient-reported outcomes (e.g., functional exercise capacity, quality of life)
Coping	• Determine the relationship between the occurrence, severity, and distress of dyspnea and the use of various engagement and disengagement coping strategies • Evaluate how the use of different coping strategies influences the impact of dyspnea on patient-reported outcomes (e.g., functional exercise capacity, quality of life)

Chapter 3

Systematic Review of the Literature on the Occurrence and Characteristics of Dyspnea in Oncology Patients

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ABSTRACT

Background: Dyspnea is a common and distressing symptom for oncology patients. However, dyspnea is not well-characterized and often underestimated by clinicians. This systematic review summarizes the prevalence, intensity, distress, and impact of dyspnea in oncology patients and identifies research gaps.

Methods: A search of all of the relevant databases was done from 2009 to May 2022. A qualitative synthesis of the extant literature was performed using established guidelines.

Results: One hundred-seventeen studies met inclusion criteria. Weighted grand mean prevalence of dyspnea in patients with advanced cancer was 58.0%. Intensity of dyspnea was most common dimension evaluated, followed by the impact and distress. Depression and anxiety were the most common symptoms that co-occurred with dyspnea.

Conclusion: Numerous methodologic challenges were evident across studies. Future studies need to use valid and reliable measures; evaluate the impact of dyspnea; and determine biomarkers for dyspnea.

Keywords: biomarkers; breathlessness; cancer; dyspnea; shortness of breath; systematic review

INTRODUCTION

Dyspnea is an extremely distressing symptom [1] that has a negative impact on oncology patients' QOL and in some cases is associated with decreases in survival. [2] Despite its tremendous burden, dyspnea is often underestimated by clinicians. [3] For example, while clinicians reported that less than 30% of patients with lung cancer experienced moderate to severe dyspnea, over 50% of their patients reported the occurrence of this symptom. [4]

One possible explanation for this discrepancy between patients' and clinicians' appraisals of dyspnea is the large amount of inter-individual variability in its occurrence across various types of cancer. In patients with lung cancer [4-6] or advanced cancer, [7-9] the prevalence rates for dyspnea range from 10% to 90%. Factors that contribute to this variability include: gender, cancer types, presence of metastatic disease, receipt of previous cancer treatment(s), smoking history, environmental factors, comorbidities, [1] and/or presence of co-occurring symptoms. [7] However, exact prevalence rates and associated risk factors in patients with other types of cancer warrant additional investigation.

While guidelines published by the ATS, [10] the NCCN, [11] and the ASCO [12] all use the term "dyspnea", the definition of this symptom, as well as the terms that should be used to assess its occurrence, severity, distress, and impact are not standardized. [13] Of note, patients use a variety of words to describe dyspnea (e.g., "shortness of breath", "difficulty breathing", "chest tightness", "air hunger" [7, 10, 13, 14]). This lack of a standardized nomenclature is a significant limitation to be able to make comparisons across studies [15] and develop a comprehensive symptom assessment instrument.

Dyspnea is a multidimensional symptom that warrants evaluation using the domains of sensory-perceptual experience, affective distress, and impact. [10] While a number of measures are used routinely in dyspnea research (e.g., MRC Dyspnea scale, [16-19] Modified Borg scale, [20-22] NRS [23-25]), most of them do not assess the multiple dimensions of patient's experience with dyspnea. [10, 12] In addition, because most of the dyspnea measures were

developed before the ATS published their consensus definition, [10] very few measures have included an assessment of the affective dimension of dyspnea. [26-30]

Taken together, no consensus exists on the specific instruments to use to assess the occurrence, severity, distress, and/or impact of dyspnea in oncology patients. To date, the only systematic review of dyspnea in oncology patients focused solely on patients with lung cancer. [31] This limitation is a significant one because in a cross-sectional study of dyspnea in 923 oncology patients, [1] only 9.4% had primary and metastatic lung cancer. The remaining 90.6% of patients with heterogeneous types of cancer experienced dyspnea from a variety of factors (e.g., cancer treatment(s), comorbid conditions). Given the paucity of research on the prevalence, severity, distress, and impact of dyspnea in oncology patients, this systematic review was undertaken to answer the following questions: 1) What are the most common terms used to assess for dyspnea?; 2) What are the most common instruments used to assess for dyspnea?; 3) What are the most common dimensions of the symptom experience that are used to describe dyspnea?; 4) What are the most common risk factors for dyspnea?; 5) What are the most common outcomes that are evaluated in studies that assess dyspnea?; 6) What are the most common co-occurring symptoms associated with dyspnea?; 7) What is the relationship between stress and dyspnea?, and 8) What are the most common biomarkers associated with dyspnea?

METHODS

This systemic review was registered with the International Prospective Register of Systematic Reviews (CRD42021284183). The PRISMA-P statement was used to perform this review. [32, 33] Studies that were published between January 1, 2009 and May 31, 2022 were retrieved. The search strategy for each database is listed in Table 1.

Eligibility criteria

Inclusion criteria

Studies were selected using the criteria listed in Table 2. Case-control and cohort studies that had either a cross-sectional or longitudinal design, as well as RCTs were included. Peer-reviewed, full-text articles in English were included. No restrictions were imposed related to cancer types or treatments.

Exclusion criteria

Studies published in languages other than English and the grey literature were excluded. Studies of pediatric and adolescent (<18 years old) patients with cancer, as well as studies that investigated dyspnea in patients with other respiratory conditions (e.g., COPD, respiratory infections) were excluded. Studies of hospice and terminally ill patients were excluded. Studies that evaluated dyspnea using the Common Terminology Criteria for Adverse Events were excluded.

Information sources and search strategy

In collaboration with a medical librarian, literature search strategies were developed using MeSH terms and various text words related to dyspnea in adult oncology patients. The following databases were searched: Cochrane Library, PubMed, Embase, Web of Science, and CINAHL. This search was conducted in October 2021 and re-run immediately before completing the data extraction and the final analysis. We hand-searched reference lists of full-text manuscripts and cross-referenced them for potentially relevant papers.

Data management

Literature search results were uploaded to the Endnote reference management software and duplicates were removed. All retrieved studies were imported into Covidence (Veritas Health Innovation, Melbourne, Australia) a web-based systematic review program. The research team used Covidence to screen the titles, abstracts, and full text of the imported references. In addition, Covidence created the PRISMA flow diagram (Figure 1).

Selection process

Using Covidence, two reviewers (JS and CM) independently screened the titles and abstracts created by the search based on the prespecified inclusion and exclusion criteria. Then, two reviewers (JS and CM) reviewed the full text of articles to clarify the inclusion of studies that could not be determined through only a review of the abstract. Full-text articles that met the inclusion criteria were retrieved. Inter-rater agreement was 0.43 for the title and abstract screening and 0.50 for the full text review. The two reviewers (JS and CM) resolved disagreements through discussion with a third independent reviewer. In addition, two reviewers (JS and CM) recorded the reasons for excluding articles (see Figure 1).

Main outcomes

The primary outcomes for this systematic review were to: 1) determine the standardized nomenclature for dyspnea in patients with cancer; 2) determine the prevalence of dyspnea in patients with cancer; 3) identify the most common risk factors for dyspnea in patients with cancer; 4) determine the most common dimensions of the symptom experience that were used to describe the experience of dyspnea in patients with cancer; 5) evaluate the most common patient reported outcomes associated with dyspnea in patients with cancer; 6) evaluate for co-occurring symptoms associated with dyspnea in patients with cancer; 7) determine the relationship between stress and dyspnea in patients with cancer; and 8) determine the most common biomarkers associated with dyspnea in patients with cancer.

Risk of bias in individual studies

The methodological quality of each of the studies was examined using the NHLBI National Institute of Health Quality Assessment Tool for Observational and Cross-Sectional Studies (Supplemental Table 1). [34] Questions on this tool were designed to enable researchers to critically appraise the internal validity of various types of research studies. Each question was answered with a ‘yes’, ‘no’ or ‘cannot determine, not reported or not applicable’ choice. Items that received ‘no’ or indeterminable responses were considered study

weaknesses that could introduce bias. As recommended by the NHLBI guidelines, this potential risk of bias must be further evaluated by a reviewer and be factored into the final rating of 'good', 'fair' or 'poor'. Two reviewers (JS and CM) independently assessed the quality of each study and combined their results in a shared excel spreadsheet. All studies that met the inclusion and exclusion criteria were included in this review regardless of the methodological quality assessment rating.

Data extraction and synthesis

A qualitative synthesis of the quantitative studies is reported for this systematic review. The data from each study were extracted based on pre-specified review criteria. Our pre-specified review criteria included: author(s); year of publication; study aims; study design; sample size; patient characteristics (e.g., age, sex, ethnicity/race, employment status, smoking status, functional status, inpatients/outpatient status, cancer diagnosis, cancer treatment(s), treatment(s) for dyspnea, the timing of symptom assessment(s)); study methods (e.g., symptom instrument(s), symptom dimensions); study outcomes (e.g., risk factors, prevalence, QOL, impact); evaluation of additional outcomes (e.g., co-occurring symptoms, stress measures, biomarkers); and the study's strengths and limitations. The data were organized using three tables (i.e., one for cross-sectional studies (Supplemental Table 2); one for longitudinal studies (Supplemental Table 3); one for the enrollment data from RCTs (Supplemental Table 4). Two reviewers (JS and CM) tested the data extraction tables with three studies in each category and revised the tables accordingly to optimize data extraction. These tables were used to synthesize the findings from this review.

RESULTS

Study selection

The initial search resulted in 7456 articles. Following the removal of duplicates, 5841 articles remained. Next, the title and abstract of each study were reviewed against our inclusion and exclusion criteria and 5614 studies were excluded. Two reviewers (JS and CM) reviewed

the full text of the remaining 227 articles against the inclusion and exclusion criteria. Following these steps, 112 articles were retained for data extraction. Five articles that were identified by the hand-searching process were added to this systematic review. A total of 117 articles is included in this systematic review (i.e., 29 cross-sectional (24.8%), 44 longitudinal (37.6%), 44 RCTs (37.6%)).

Methodological quality of studies

All of the cross-sectional and longitudinal studies received a 'good' quality rating. Of note, only 31 of the 44 RCTs received a 'good' quality rating and 13 received a 'fair' rating. Across the 13 studies that received a 'fair' rating, the most common sources of bias were: 1) participation rate of eligible persons was <50%; 2) outcome assessors were not blinded to the exposure status of participants; 3) loss to follow-up after enrollment was >20%; and 4) key potential confounding variables were not measured and/or not adjusted for in the statistical analyses.

Study characteristics

Of the 117 studies included in this review of dyspnea in oncology patients, forty one studies were conducted in the United States, [4, 7, 17, 23, 35-62, 64-71] sixteen in England, [9, 14, 18, 21, 28, 72-82] nine in Canada, [9, 75, 83-89] seven in Italy, [9, 22, 56, 75, 90-92] seven in Germany, [24, 53, 90, 93-96] seven in South Korea, [5, 56, 97-101] seven in China, [102-108] six in Spain, [9, 75, 109-112] five in Turkey, [16, 113-116] five in Japan, [19, 25, 117-119] four in Denmark, [9, 90, 120, 121] four in Sweden, [90, 122-124] three in Norway, [9, 90, 125] three in Switzerland, [9, 75, 90] three in Australia, [9, 126, 127] two in Finland, [90, 128] two in Hong Kong, [100, 129] two in Taiwan, [100, 130] and two in Austria. [56, 131] The remaining studies were conducted in India, [132] Indonesia, [20] New Zealand, [133] and other Asian [100] and European [9, 56, 90, 134] countries.

Sample sizes ranged from 12 [134] to 27,795. [72] Across these studies, the majority of patients were elderly (weighted grand mean age of 69.7 years), male (weighted grand mean

proportion of males, 54.5%), outpatients, and previous or current smokers. Most patients had advanced cancer and their weighted grand mean KPS scale score was 70.0. Forty-four studies evaluated for respiratory comorbidities. COPD was the most common respiratory disease. Forty studies evaluated for dyspnea in patients receiving cancer treatments (i.e., chemotherapy in 25 studies, [4, 17, 19, 36, 40, 42, 44, 56, 69, 71, 79, 81, 90, 95, 100, 101, 103, 105, 110, 116, 117, 124, 128, 130, 134, 135] radiotherapy in 8 studies (palliative radiotherapy in 5 studies), [18, 46, 52, 70, 85, 86, 114, 129] thoracic surgery in 4 studies, [51, 91, 92, 107] curative-intent lung cancer treatment in 2 studies, [38, 45] allogeneic hematopoietic stem cell transplantation in 1 study [113]).

Nomenclature for dyspnea symptom

Seventy-four studies (63.2%) used dyspnea, 27 (22.9%) used breathlessness, six (5.2%) used shortness of breath, and one study (0.7%) used difficulty breathing to measure dyspnea. In addition, six studies (5.2%) used both dyspnea and shortness of breath and one study (0.7%) used both dyspnea and breathlessness. The other two studies (1.7%) used three terms: dyspnea, shortness of breath, and difficulty breathing, interchangeably.

Prevalence of dyspnea

The weighted grand mean prevalence of dyspnea in patients with advanced cancer was 58.0%. The weighted grand mean prevalence of dyspnea in patients with lung cancer was 34.9%. Among these samples, 48.2% of patients with cancer experienced moderate to severe dyspnea. In addition, 45.5% of oncology patients with dyspnea reported breakthrough, episodic, or exertional dyspnea.

Common dimensions of the dyspnea experience

The most common symptom dimension used to assess dyspnea was intensity (i.e., 110 out of 117 studies (94.0%)), followed by impact in 42 studies (35.9%), occurrence in 37 studies (31.6%), distress in 13 studies (11.1%), and frequency in 4 studies (3.4%). Among the 40 studies that evaluated only one dimension of the symptom experience, 33 studies used

intensity, [17-25, 44, 51, 55-57, 62, 65, 70, 75, 78, 79, 90, 93, 100, 102, 103, 109, 112, 118, 121, 125, 129, 130, 135] five evaluated occurrence, [72, 74, 76, 117, 131] and one evaluated impact. [106] No studies were identified that evaluated distress as a single dimension of the symptom experience. Of the 50 studies that assessed two dimensions of dyspnea, 22 used occurrence and severity, [5, 9, 35, 41, 42, 47, 48, 50, 52-54, 83-86, 89, 98, 99, 104, 105, 114, 132] 22 used severity and impact, [16, 36, 38, 43, 45, 49, 68, 69, 73, 87, 94, 95, 97, 101, 107, 108, 111, 113, 116, 120, 128, 134] five used severity and distress, [14, 39, 64, 81, 115] and one used occurrence and impact. [37]

Common measures of dyspnea

Occurrence

Of the 37 studies that evaluated the occurrence of dyspnea, nine used the ESAS, [7, 48, 52, 83-86, 89, 114] five used the LCSS scales, [4, 35, 40, 104, 110] four used the EORTC-QLQ-C30 [99, 124] and/or LC13, [42, 105] two used the MSAS, [67, 96] two used the NRS, [9, 50] and two used the modified Borg scale. [53, 54] The other four studies used the MDASI, [41] MRC dyspnea scale, [5] SYMPTOM lung questionnaire, [76] and BDI. [37] The remaining nine studies obtained the occurrence rate for dyspnea from the medical record. [47, 72, 74, 91, 92, 98, 117, 131, 132]

Domain of sensory-perceptual experience - Intensity

The MRC dyspnea scale [5, 16-19, 36, 65, 69, 87, 88, 91, 92, 94, 98, 101, 104, 107, 108, 113, 122, 123, 126, 134] and the modified Borg scale [20-22, 49, 53, 54, 62, 64, 66, 71, 77, 80, 81, 87, 95, 96, 111, 113, 115, 116, 125, 133] that was used in each 23 of 117 studies were the most common measure used to assess intensity, followed by the NRS in 21 studies, [9, 14, 23-25, 28, 39, 50, 58, 59, 61, 62, 66, 77, 80-82, 118, 119, 126, 127] the EORTC-QLQ-C30/LC13 in 21 studies, [38, 42, 45, 60, 70, 75, 87, 90, 93, 95, 97, 99, 103, 105, 120, 121, 124, 125, 128, 130, 135] and the ESAS in 18 studies. [7, 39, 48, 52, 59, 60, 64-66, 83-86, 89, 109, 112, 114, 128] Ten studies used the LCSS, [4, 35, 40, 43, 44, 55, 56, 100, 104, 110] nine studies used the

VAS, [21, 35, 71, 78, 79, 115, 119, 129, 133] three used the MDASI, [41, 102, 118] and three used the UCSD SOBQ. [38, 45, 57] In addition, two studies used the CRQ, [73, 80] two used the MSAS, [67, 68] and one used the OCD. [88]

Domain of affective distress

Among the 13 studies that evaluated distress associated with dyspnea, eight used the NRS; [14, 28, 64, 77, 80-82, 127] and two used the VAS [115, 126] (Figure 5). The other three studies used the modified Borg scale, [66] MSAS, [67] and RDOS. [39]

Frequency

Only four studies measured the frequency of dyspnea. Of these four studies, two used the MSAS, [67, 96] one an ad-hoc questionnaire (i.e., the frequency of shortness of breath during the last 24 hours: never, rarely, occasionally, frequently, or continually), [110] and one personal interviews (i.e., per day, per week, or per month). [53]

Domain of dyspnea impacts

In terms of functional exercise capacity associated with dyspnea, 20 studies used the 6MWT. [16, 36, 38, 45, 87, 88, 91, 92, 94, 95, 101, 106-108, 113, 122, 123, 126, 133, 134] To evaluate interference with daily activities, three studies used the OCD, [7, 69, 134] one used the BDI, [37] and one used the task avoidance item related to dyspnea from the PROMIS measures. [68] In addition, one study assessed the impact of dyspnea on occupational performance, using the AMPS and the IPPA. [120] The other study used an ad-hoc questionnaire to evaluate dyspnea's level of interference with physical, psychological, and social aspects of patients' daily lives. [110]

In terms of associations between dyspnea and QOL, three studies used EORTC-QLQ-C30, [97, 124, 128] three used the FACT-L scale, [4, 40, 71] and two used the CRQ, [73, 80] The remaining three studies used the Short Form Six-Dimension (SF-6D), [49] LCSS, [28] and the linear analogue self-assessment scale. [43] In addition, two studies used the BODE index

(i.e., body mass index, FEV1, 6-MWT distance, modified MRC dyspnea scale) to evaluate dyspnea as a prognostic factor. [36, 94]

Multidimensional measures

Of the 32 studies that used multidimensional measures, ten used multidimensional dyspnea measures, namely: CDS in seven studies, [19, 39, 59-61, 66, 71] and the D-12 scale in three studies. [28, 82, 133] Eight studies used the ESAS to measure dyspnea occurrence and intensity. [7, 48, 52, 84-86, 89, 114] In addition, six studies used the EORTC-QLQ-C30 and/or LC13 to measure dyspnea occurrence, intensity, and/or impact. [42, 97, 99, 105, 124, 128] Five used the LCSS to measure dyspnea occurrence and intensity. [4, 35, 40, 104, 110] Two used the MSAS to evaluate the occurrence, intensity, frequency, and/or distress of dyspnea. [67, 96] One study used the BDI to measure the occurrence and impact of dyspnea. [37]

Common risk factors for dyspnea

Nineteen studies identified risk factors associated with dyspnea. Sixteen studies (84.2%) examined factors that impact the severity of dyspnea, [6, 7, 9, 18, 38, 41, 46, 83-85, 89, 90, 93, 114, 124, 128] and three (15.8%) examined factors associated with the occurrence of dyspnea. [37, 86, 98]

Demographic and clinical characteristics associated with the occurrence of dyspnea

Older age, being unemployed, having a lower education level, and not engaging in moderate to strenuous physical activity were associated with higher dyspnea occurrence rates. [37] In addition, a history of tobacco use, [37, 98] lower performance status, [98] lower pulmonary function test scores, [37, 98] as well as the occurrence of pulmonary comorbidity, [37] and preoperative dyspnea, [37] were associated with higher occurrence rates of dyspnea. In addition, patients with depressive symptoms were more likely to report dyspnea. [37]

Demographic and clinical characteristics associated with severe dyspnea

Older age, [9, 38, 84, 89, 124] being male, [84, 89, 124] being single, [9] having a lower educational level, [93] having a lower income, [89, 93] having a higher socioeconomic

marginalization score, [84] being an immigrant, [84] and not engaging in physical activity [46, 93] were associated with severe dyspnea. In contrast, in two studies, younger age, [41] being female, [41] and not being an immigrant [89] were associated with severe dyspnea. In the remaining two studies, [46, 128] no associations were found between demographic characteristics (i.e., age, gender) and the severity of dyspnea.

Being a current smoker, [93] having a lower performance status, [6, 9, 90, 124] having lost >5% of one's body weight, [124] and having a higher body mass index [9] were associated with severe dyspnea. In addition, having anemia, [114] respiratory comorbidities [85, 93, 114] (i.e., COPD [9, 83]), and heart disease [9] (i.e., cardiovascular comorbidities, [93] HFrEF [38]) were associated with severe dyspnea. Having primary or metastatic lung cancer, [9, 41, 114] having advanced stage of cancer [41] (i.e., stage III lung cancer [84, 93, 124]), currently receiving cancer treatment, [93] or having a recent medical history of lung cancer treatment [93] or thoracic radiotherapy [89, 114] were associated with severe dyspnea. While having small cell or squamous cell carcinoma was associated with severe dyspnea, [41] not having a confirmed histological diagnosis negatively impacted the severity of dyspnea. [18] In addition, having lower pulmonary function test parameters (i.e., decreased FEV1, [7, 38] DL_{CO} [38]), a pleural effusion, [114] or liver metastasis [41] were associated with severe dyspnea. Higher levels of depression, [7, 9, 93] anxiety, [9, 93] pain, [7, 9] and fatigue [7] were associated with severe dyspnea. In contrast, in two studies that evaluated a number of clinical characteristics (i.e., cancer stage, pathological diagnosis, pack-years smoked, brain or bone metastases, higher dose of radiation to the heart), [46, 128] no associations were found with the severity of dyspnea.

Common co-occurring symptoms associated with dyspnea

While 88 studies assessed co-occurring symptoms associated with dyspnea in patients with cancer, only 21 studies (23.9%) [7, 9, 14, 28, 35, 37, 39, 43, 45, 50, 52, 71-73, 83, 86, 90, 93, 111, 115, 129] reported on these associations. Depression and anxiety were the most common symptoms that co-occurred with dyspnea. For both symptoms, higher severity scores

were associated with more severe [7, 9, 28, 39, 45, 52, 71, 86, 93, 111, 115, 129] and distressing [115] levels of dyspnea. Fatigue was the second most common co-occurring symptom that demonstrated a positive relationship with dyspnea. [7, 35, 39, 52, 73, 83, 129] In four studies, [9, 52, 90, 93] positive associations were found between pain intensity and dyspnea. In two studies, [7, 39] higher levels of sleep disturbance were associated with more severe dyspnea. Interestingly, only one study reported on the co-occurrence of cough with dyspnea. [72]

Relationship between stress and dyspnea

No studies were identified that examined the relationship between dyspnea and stress in oncology patients.

Biomarkers associated with dyspnea

Of the 30 studies that evaluated biomarkers in patients with cancer, 15 studies (50%) reported on the relationship between dyspnea and biomarkers. Eight used PFTs. [5, 7, 38, 45, 98, 99, 115, 125] Three evaluated for associations between dyspnea intensity and polymorphisms in specific genes (i.e., 5-HT-HTR3B, ARRB2, BRCA1, IL-6, IL-1β). [55, 90, 105] The remaining four studies measured SpO2, [71, 114] respiratory rate, [39, 114] heart rate, [39] and arterial blood gas values. [91]

Common outcomes associated with dyspnea

Of the 50 studies that examined associations between dyspnea and a variety of patient reported outcomes, 20 studies evaluated functional exercise capacity. [16, 36, 38, 45, 87, 88, 91, 92, 94, 95, 101, 106-108, 113, 122, 123, 126, 133, 134] In addition, eleven studies evaluated QOL; [4, 28, 40, 43, 49, 71, 73, 80, 97, 124, 128] seven examined interferences with daily activities; [7, 37, 68, 69, 110, 120, 134] and 12 evaluated survivals. [9, 18, 36, 43, 49, 52, 74, 92, 94, 97, 98, 131]

Characteristics of breakthrough, episodic, or exertional dyspnea

Of the fourteen studies that evaluated for breakthrough, episodic, or exertional dyspnea, nine used the modified Borg scale, [53, 54, 61, 62, 64, 80, 109, 113, 116] two used the NRS, [24, 59] and two used the ESAS. [7, 65] The mean intensity of breakthrough dyspnea ranged from 4.9 [59] to 5.4 [64] on a 0 to 10 NRS using the modified Borg scale. In one study, [109] breakthrough dyspnea, on average, occurred 2.5 times per day, lasted for 10.2 minutes, occurred primarily during the daytime, and had gradual and unpredictable characteristics associated with a variety of exacerbating factors (e.g., movement, cough). In another study, [7] patients reported an average of 1 to 5 daily episodes of breakthrough dyspnea that lasted 2 to 10 minutes. In two studies, [53, 54] the median duration of episodic dyspnea was 5.0 minutes and 56% of the patients experienced this symptom 1 to 3 times per day.

DISCUSSION

This systematic review is the first comprehensive evaluation of thirteen years of research on dyspnea in patients with cancer. Guided by eight questions, the overall goals of this review were to provide a detailed picture of this symptom for clinicians caring for oncology patients and to identify gaps that could be used to guide future research. This discussion focuses on the major findings and limitations associated with the extant literature and provides recommendations for future research on dyspnea in patients with cancer.

Nomenclature for dyspnea symptom

While 63.6% of the studies in this review used the term “dyspnea”, variations in terminology occurred across countries. For example, most of the studies that used the term “breathlessness” were performed in European countries [9, 90] (e.g., the United Kingdom [14, 18, 73, 74, 76, 77, 80, 81]). This finding may be explained by the fact that the European Society for Medical Oncology’s clinical practice guideline on the management of dyspnea in oncology patients [136] used the term “breathlessness”. While cultural and linguistic differences may exist in describing this symptom, it is worth noting that an ongoing debate exists in the literature on

whether distinct mechanisms underlie dyspnea versus breathlessness. [13, 137] In addition, standardized definitions for various subtypes of dyspnea (e.g., breakthrough, episodic, exertional) do not exist. [109] As a result, of the 14 studies included in this review that evaluated breakthrough, episodic, or exertional dyspnea, [7, 24, 53, 54, 59, 61, 62, 64, 65, 80, 109, 113, 116] all of them used different operational definitions.

Prevalence of dyspnea

Consistent with the findings from the previous review, [31] a wide variety of instruments with different scales, as well as inconsistent definitions and different assessment time frames, were used to determine the occurrence rates for dyspnea. This heterogeneity does not allow for a meta-analysis to obtain more precise estimates of the prevalence of this symptom in patients with cancer. Equally important, while the weighted grand mean prevalence of dyspnea in patients with advanced cancer was higher than in patients with lung cancer, prevalence rates for patients with other types of cancer are not well characterized. In addition, our findings suggest relatively high rates of moderate to severe dyspnea, as well as breakthrough, episodic, and/or exertional dyspnea. Based on these findings, oncology clinicians need to assess for dyspnea in patients with heterogeneous types of cancer.

Risk factors for dyspnea

Significant risk factors for dyspnea that were identified in the multivariable regression analyses included: age, [41, 84, 89] lower socioeconomic status, [9, 84, 89, 93] lower functional status, [6, 9, 85, 90, 124] sedentary lifestyle, [37, 93] the occurrence of cardiopulmonary comorbidities, [9, 38, 85, 93] the presence of advanced-stage cancer, [41, 84, 93, 124] the occurrence of lung metastasis, [9] a history of cancer treatment, [89, 93] as well as the occurrence of anxiety or depression. [7, 9, 37, 45, 86, 93] However, these findings need to be interpreted with caution because the results were not always consistent (e.g., younger [41] versus older age [9, 37, 38, 84, 89, 124]); sample sizes in some studies were relatively small; [6, 7, 38, 46] the overall number of studies that assessed for risk factors was limited; and none of

the studies assessed a comprehensive list of risk factors in the same sample. In addition, no studies were identified that evaluated for risk factors associated with higher levels of distress or interference from dyspnea.

Dyspnea symptom dimensions

Given that the 2012 ATS official statement [10] proposed that sensory-perceptual, affective distress, and impact dimensions of dyspnea warrant evaluation, a significant limitation in the studies included in this review is that intensity was the most common dimension assessed (i.e., 94.1% of studies). Of note, only 11% and 35.6% of the studies evaluated affective distress and impact, respectively. An important aspect of the sensory domain is an evaluation of patients' descriptions of the qualities of dyspnea (e.g., "stuck in the airway", "shallow", "breathing difficulty", "distressing"). This type of evaluation may help to infer different etiologies for dyspnea and increase one's understanding of patients' experiences of dyspnea. [13, 29, 137] However, only 8.5% of studies included in this review evaluated the sensory qualities of this symptom. This omission is significant, given that the ATS definition of dyspnea consists of qualitatively distinct sensations that vary in intensity. [10] The use of instruments like the CDS and the D-12 would allow for a more comprehensive assessment of the various domains of dyspnea. [28, 71]

Dyspnea measures

A large amount of variability existed in the measures that were used to assess dyspnea. This variability is most likely related to a lack of consensus on the operational definition of dyspnea and a lack of guidance on how to choose the most valid and reliable measures to assess dyspnea in patients with cancer. Our findings suggest that most researchers selected instruments that demonstrated validity and reliability in patients with COPD.

Unidimensional Scales

While unidimensional scales can be rated easily by oncology patients because of their simplicity, [12] as noted previously, [10] it is not clear whether these scales are evaluating the severity or distress of dyspnea. To balance these benefits and limitations, twelve studies

assessed dyspnea using unidimensional scales with clearly specified dimensions [14, 64, 66, 77, 80, 112, 115, 126] and time frames. [77, 81, 82, 127] For example, in four studies that used a 0 to 10 NRS, [77, 81, 82, 127] dyspnea was measured at its best, at its worst, on average, and/or now. In addition, in one study, [127] distress associated with dyspnea, as well as perceived control over dyspnea were evaluated. Of note, in order to identify high risk patients, as well as to be able to evaluate the efficacy/effectiveness of interventions, clinically meaningful cutpoints for different dimensions of dyspnea (e.g., intensity, distress, impact) need to be determined. In addition, the modified MRC dyspnea scale, the most commonly used measure among the studies in this review, assesses the intensity of dyspnea associated with daily activity. [138] Two studies used the modified MRC dyspnea scale with the ESAS [65] or LCSS [104] to measure the intensity of average dyspnea and dyspnea on exertion concurrently. These studies suggest that an evaluation of dyspnea at rest and on exertion can occur in a single study.

Multidimensional Scales

While a large amount of heterogeneity existed, 76 studies used multidimensional scales to assess dyspnea in patients with cancer. Of note, the CDS and D-12 are the only two multidimensional instruments that were validated in oncology patients. [26, 28, 71] However, in terms of the use of these two multidimensional measures, several points warrant consideration. First, while the CDS evaluates three factors (i.e., sense of effort, discomfort, and anxiety), ongoing debates exist about the interconnectedness of these factors and their weak convergent validity. [26, 29, 71] In addition, the MCID for CDS scores is not established. [26, 28, 71] Second, the CDS and D-12 may not be suitable for an evaluation of dyspnea on exertion or at a specific time. [29] However, it is interesting to note that in one study, [28] strong and positive correlations were found between D-12 scores and ratings of average and worst dyspnea using a NRS. [28] Another limitation is that neither the CDS nor the D-12 include an evaluation of the impact of dyspnea. The addition of a QOL measure (e.g., short form CRQ, [139] EORTC QLQ-

C30/LC13 [124, 128]) may help to overcome this limitation. In addition, the concurrent use of the MSAS would allow for an evaluation of four different dimensions of dyspnea (i.e., occurrence, frequency, intensity, distress). [67]

Co-occurring symptoms associated with dyspnea

The HADS [7, 37, 45, 111, 115] and ESAS [7, 39, 52, 86] were the most common measures used to assess anxiety and depressive symptoms. While findings were inconsistent, the data suggest that anxiety and/or depression have a stronger association with distress (i.e., affective dimension) [111, 115, 129] than with intensity (i.e., sensory-perceptual dimension) ratings. [7, 39]

The ESAS was the most common measure used to evaluate fatigue associated with dyspnea. In terms of the co-occurrence of dyspnea and fatigue, four studies [16, 39, 77, 103] proposed that advanced cancer and its treatment caused respiratory muscle fatigue in patients with cancer. This hypothesis is supported by the finding that patients who reported the co-occurrence of these two symptoms had a lower exercise tolerance for daily activities (i.e., lower values in the OCD). [7]

In terms of dyspnea and pain, a number of hypotheses exist to explain this association. For example, pain may increase ventilatory drive, that results in breakthrough dyspnea. [7] In addition, pain frequently co-occurs with anxiety, which may be associated with an increase in the intensity of dyspnea. [9] In terms of cough, three studies reported on the symptom cluster of dyspnea, cough, and fatigue. [43, 141, 142] While only one study found a positive association between the occurrence of dyspnea and cough, [72] in another study, [109] cough was associated with breakthrough dyspnea.

Role of stress and resilience in dyspnea

A plausible hypothesis to explain the relationship between stress and dyspnea is that stress activates the HPA axis. [143] This dysregulation results in negative immunological, metabolic, and neuropsychological sequelae, [143-146] that contribute to increases in

dyspnea's severity and/or distress. However, no studies have evaluated for associations between dyspnea and stress in oncology patients. Given the evidence that cancer and/or its treatments can result in alterations in immune system function and HPA axis activity, [147-149] an investigation of the impact of stress on patients' experiences with dyspnea is warranted. In terms of resilience, five studies evaluated perceived control over dyspnea using a NRS; [127] ability to cope with dyspnea using a NRS; [77, 82] or a mastery item from the CRQ. [73, 80] However, no studies evaluated for direct relationships between dyspnea and resilience in oncology patients.

Biomarkers associated with dyspnea

Among the various PFTs, FEV1 was the most common biomarker evaluated. While four studies reported negative associations between the intensity of dyspnea and FEV1 values, [7, 38, 98, 115] in two studies, [5, 45] a reduced FEV1 value was associated with worse prognosis in patients with dyspnea who received treatment for lung cancer. A reduction in FEV1 may be an indicator of obstructive ventilatory defects (e.g., thoracic tumors, [150] pulmonary toxicities [151]) or COPD. While MIP can be used to measure the strength of inspiratory muscles [152] and D_{LCO} may be useful to evaluate for impaired gas exchange, [153] the use of these biomarkers in oncology patients with dyspnea is limited. In addition, given that anemia effects the oxygen-carrying capacity of the blood and oncology patients are more likely to experience this condition, it is interesting to note that no studies evaluated for associations between dyspnea and hemoglobin levels. [10] In two studies that examined the associations between dyspnea and SpO2, while one reported no association, [39] the other study reported that lower oxygen saturation levels were associated with increases in discomfort. [71] However, no association was identified between SpO2 and anxiety. [71]

Of the three studies that evaluated for associations between the severity of dyspnea and several single nucleotide polymorphisms, it is interesting to note that in one study, [90] individuals who were homozygous for the rare allele in the serotonergic subtype receptor gene

reported more severe dyspnea. Given the evidence that suggests a role for the 5-HTTLPR genotype in fearful dyspnea anticipation, [154] this finding suggest that the HTR3B polymorphism may modify biological and psychological interactions between the sensory-perceptual and affective components of dyspnea. However, additional studies with a variety of molecular markers (e.g., candidate genes, gene expression, DNA methylation) are warranted to elucidate the underlying mechanisms for dyspnea.

Impact of dyspnea

Functional exercise capacity

In one study that used the 6MWT to measure functional exercise capacity postoperatively in patients with early-stage lung cancer, [38] dyspnea was an independent predictor of decreases in this measure. The ATS guidelines for the 6MWT state that the test reflects systemic responses during exercise that include the pulmonary and cardiovascular systems, as well as muscle and systemic metabolism. [155] Given the paucity of research, the utility of the 6MWT to evaluate the impact of dyspnea in oncology patients warrants additional investigation. For example, about 20% of patients with a modified MRC scale score of 4 could not complete the 6MWT and 75% of these patients could not complete the 2-minute walk test. [126] Alternatively, the OCD may be a useful measure to evaluate subjective exercise tolerance with daily activity. Previous studies of patients with airway obstruction or pulmonary infiltration demonstrated a strong correlation between the OCD and 6MWT. [63, 140]

Interference with daily activities

In one study that used the OCD, [7] dyspnea was associated with moderate to severe interference with walking, normal work, enjoyment of life, mood, and general activity. While in two studies, [102, 118] the MDASI was used to measure dyspnea intensity, neither paper reported on interference scores associated with dyspnea. In addition, no studies attempted to cluster the sub-items of dyspnea interference depending on physical and emotional function. Given the multifactorial nature of dyspnea, efforts to cluster similar dimensions of daily

functioning may be beneficial to increase our understanding of the impact of dyspnea on daily activities and how to develop more targeted interventions.

QOL

While a variety of QOL measures were used, our findings identified that higher levels of dyspnea were associated with worse QOL. Specifically, dyspnea had a significantly negative effect on physical function. [128] In addition, in one study, [43] higher dyspnea occurrence rates were associated with higher rates of unemployment and lower rates of physical activity. In another study, [49] greater improvements in dyspnea were associated with increases in QOL.

Survival and prognosis

While one study reported no relationship between dyspnea severity and survival, [97] in five studies, [9, 18, 49, 52, 98] as the severity of dyspnea increased survival decreased. In addition, in three studies, [43, 98, 131] increases in the occurrence rates for dyspnea were associated with decreased survival rates. These findings suggest that dyspnea is a significant prognostic factor in patients with cancer. This hypothesis is supported by one study that found a positive relationship between the BODE index score and mortality risk in patients with inoperable non-small-cell lung cancer. [36]

LIMITATIONS

Several limitations warrant consideration. First, this review may have a potential publication bias because the grey literature was excluded. However, the grey literature may have methodological drawbacks and lack peer review. Second, this review was limited to articles written in English. In addition, no meta-analysis was done because of the lack of homogeneity in the study samples and dyspnea measures.

CONCLUSIONS

Despite its limitations, this review identified significant methodologic challenges in the field, as well as gaps in knowledge that can be used to guide future research (Table 3). In terms of methodologic challenges, the operational definitions of dyspnea (i.e., consistent and

linguistically appropriate terminology), as well as the definitions and characteristics of the associated subtypes of dyspnea (e.g., breakthrough, episodic) need to be established. Valid and reliable measures of the sensory, affective, and impact dimensions of dyspnea need to be developed for oncology patients. These measures need to be comprehensive and sensitive to change. In terms of research, several areas for consideration are summarized in Table 3. Finally, in order to develop effective interventions for dyspnea, the mechanism(s) that underlie this symptom warrant investigation.

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Figure 3.1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram to determine the final selection of studies that evaluated for dyspnea in patients with cancer, 2009-2021.[1]

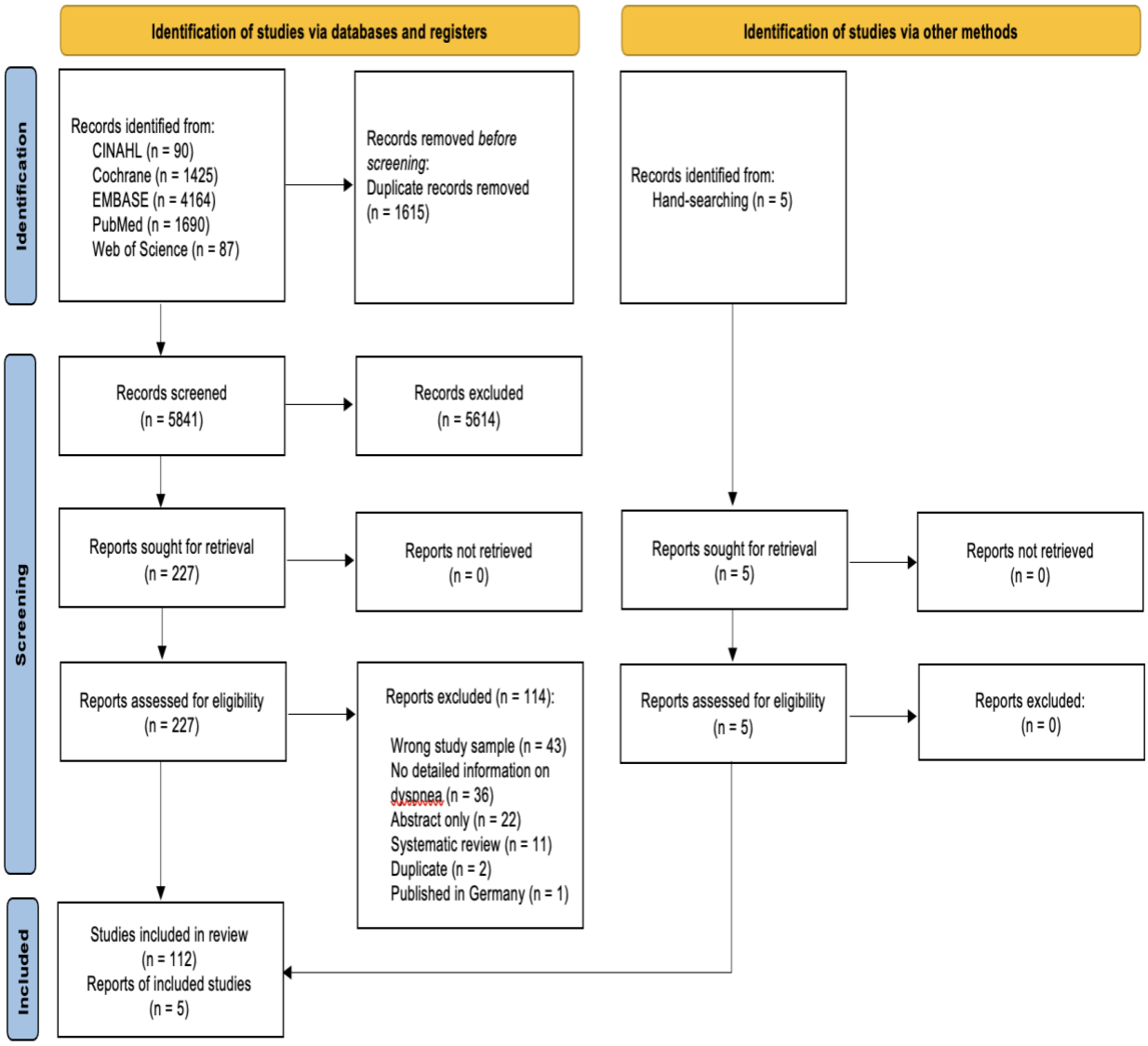

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Table 3.1. Summary of search strategy

Database	Search terms
Cochrane Library	("breathlessness" OR "dyspnea" OR "difficulty breathing" OR "labored breathing" OR "difficult breathing" in All Text) AND (cancer OR neoplasm in All Text) NOT reviews NOT protocols. Search restricted to 1 January 2009 to 31 May 2022; Language: English
Cumulative Index to Nursing and Allied Health Literature	(dyspnea OR breathlessness OR "shortness of breath" OR "labored breathing" OR "difficulty breathing" OR "difficult breathing") AND (cancer OR neoplasms) AND adult AND (“randomized controlled trial” OR “randomised controlled trial” OR RCT OR longitudinal OR “cross-sectional study” OR “cohort studies” OR “cohort study”) Search restricted to 1 January 2009 to 31 May 2022; Language: English
Embase	('dyspnea'/exp OR dyspnea OR 'labored breathing') AND ('malignant neoplasm'/exp OR 'malignant neoplasm') AND ('adult'/exp OR adult) AND (rct OR 'randomized controlled trial'/exp OR 'randomized controlled trial' OR 'randomized controlled trial (topic)'/exp OR 'randomized controlled trial (topic)' OR 'longitudinal study'/exp OR 'longitudinal study' OR 'cross-sectional study'/exp OR 'cross-sectional study' OR 'cohort analysis'/exp OR 'cohort analysis') AND [2009-2022]/py; Language: English
PubMed	(dyspnea OR "Dyspnea"[Mesh] OR breathlessness OR "shortness of breath" OR "labored breathing" OR "difficulty breathing" OR "difficult breathing") AND (cancer OR neoplasms OR "Neoplasms"[mesh]) AND (adult OR "Adult"[mesh]) AND (“randomized controlled trial” OR “randomised controlled trial” OR RCT OR "Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh] OR longitudinal OR "Longitudinal Studies"[Mesh] OR cross-sectional OR "Cross-Sectional Studies"[Mesh] OR “cohort studies” OR “cohort study” OR "Cohort Studies"[Mesh]) Search restricted to 1 January 2009 to 31 May 2022; Language: English
Web of Science	(dyspnea OR breathlessness OR "shortness of breath" OR "labored breathing" OR "difficulty breathing" OR "difficult breathing") AND (cancer OR neoplasms) AND adult AND (“randomized controlled trial” OR “randomised controlled trial” OR RCT OR longitudinal OR “cross-sectional study” OR “cohort studies” OR “cohort study”) Search restricted to 1 January 2009 to 31 May 2022; Language: English

Table 3.2. Inclusion criteria

- Population: adult patients (≥ 18 years old) with cancer
    - No restrictions by cancer types and types of cancer treatment
    - Studies of hospice and terminally ill patients were excluded
- Symptom of interest: Dyspnea, breathlessness, shortness of breath
- Comparison: not applicable
- Outcomes: risk factors, measures or instruments, prevalence, symptom dimensions, symptom outcomes (e.g., quality of life, functional exercise capacity, survival), stress, multiple co-occurring symptoms, biomarkers)
- Study design: cross-sectional studies, longitudinal studies, randomized controlled trials (only enrollment data)
- Published in a peer-reviewed journal in English
- Published between 1 January 2009 and 31 May 2022

Table 3.3. Recommendations for Future Research on Dyspnea in Patients with Cancer

Topics	Recommendations
Nomenclature for dyspnea	• Establish a standardized nomenclature for studies of dyspnea • Determine linguistically appropriate terminology to assess dyspnea • Determine linguistically appropriate terminology to assess the qualities of dyspnea • Establish standard definitions for various subtypes of dyspnea
Prevalence of dyspnea	• Determine the prevalence of dyspnea in different target populations (e.g., different types of cancer, different types of cancer treatment, different stages of disease, occurrence of other comorbidities) • Evaluate how the prevalence of dyspnea changes over time
Risk factors for dyspnea	• Identify the most common risk factors associated with the occurrence, severity and distress associated with dyspnea • Identify the risk factors associated with poorer outcomes in patients with dyspnea (e.g., survival, decrements in quality of life)
Dyspnea symptom dimensions	• Develop valid and reliable measures to assess the sensory-perceptual, affective distress, and impact domains of dyspnea • Determine how the sensory-perceptual, affective distress, and impact domains of dyspnea change over time • Identify the mechanisms that underlie the sensory-perceptual, affective distress, and impact domains of dyspnea • Test interventions to decrease the sensory-perceptual, affective distress, and impact domains of dyspnea
Dyspnea measures	Unidimensional scales: • Determine clinically meaningful cutpoints for unidimensional measure of dyspnea Multidimensional scales: • Determine the minimal clinically important difference in a change in scores on existing multidimensional measures (e.g., MCID) for the CDS scores
Co-occurring symptoms associated with dyspnea	• Investigate associations between dyspnea and other co-occurring symptoms • Investigate common and distinct mechanisms that underlie dyspnea and other co-occurring symptoms
Role of stress and resilience in dyspnea	• Investigate the impact of stress on patients' experiences with dyspnea • Evaluate for direct relationships between dyspnea and resilience in oncology patients
Biomarkers associated with dyspnea	• Determine the optimal pulmonary function tests to use as a biomarker for changes in dyspnea • Evaluate for the association between the occurrence of anemia and dyspnea • Determine molecular biomarkers that can be used for the diagnosis of dyspnea; determine underlying mechanisms; and/or evaluate the efficacy of interventions
Impact of dyspnea	• Determine the most sensitive and specific measures to evaluate functional exercise capacity • Determine the most valid and reliable subjective and objective measures to use to evaluate functional interference associated with dyspnea • Determine the best measures to assess the prognosis associated with dyspnea in patients with cancer

Chapter 4

Distinct Shortness of Breath Profiles in Oncology Outpatients Undergoing Chemotherapy

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ABSTRACT

Context: Shortness of breath is a distressing symptom that occurs in 10% to 70% of oncology patients. Despite this broad range in its occurrence, little is known about inter-individual variability in shortness of breath and associated risk factors among patients receiving chemotherapy.

Objectives: Identify subgroups of patients with distinct shortness of breath profiles; evaluate for differences among these subgroups in demographic and clinical characteristics; evaluate for differences among symptom dimensions of shortness of breath, and evaluate for differences in quality of life outcomes.

Methods: Outpatients (n=1338) completed questionnaires six times over two chemotherapy cycles. Occurrence of shortness of breath was assessed using the Memorial Symptom Assessment Scale. Latent class analysis was used to identify subgroups of patients with distinct shortness of breath profiles.

Results: Four distinct shortness of breath profiles were identified (None [70.5%], Decreasing [8.2%], Increasing [7.8%], High [13.5%]). Risk factors for membership in High class included: history of smoking, self-reported diagnosis of lung disease, having lung cancer, and receipt of a higher number of cancer treatments. Compared to the None class, High class reported poorer physical, psychological, and social functioning.

Conclusions: Almost 14% of patients with heterogeneous types of cancer receiving chemotherapy had persistently high occurrence rates of shortness of breath for almost two months. In addition, compared to the Decreasing and Increasing classes, the High class' episodes of shortness of breath were more frequent and more severe. Clinicians need to assess all oncology patients for shortness of breath and provide targeted interventions.

Keywords: cancer; cough; dyspnea; latent class analysis; patient-reported outcomes; quality of life

INTRODUCTION

Shortness of breath is a common and distressing symptom that occurs in approximately 10% to 90% of oncology patients. [1-4] While many clinicians attribute this symptom only to patients with lung cancer, three cross-sectional studies demonstrated that shortness of breath is prevalent in other types of cancer. [2, 5, 6] Patients can experience shortness of breath as a result of the cancer itself, associated treatments (e.g., pulmonary toxicities [7]), and/or other cardiopulmonary conditions. [2, 5, 6]

This broad range in prevalence rates for shortness of breath suggests that a large amount of inter-individual variability exists in this symptom. [1] While two longitudinal studies found that individual trajectories of shortness of breath varied, [4, 8] and numerous demographic and clinical characteristics impacted this variability, [4] these studies evaluated patients with advanced cancer receiving palliative care near the end of life. Therefore, additional research is needed on the occurrence, severity, distress, and risk factors for shortness of breath in patients with heterogenous types of cancer undergoing active treatment.

In our recent systematic review, [9] only three studies examined factors associated with the occurrence of shortness of breath in patients with lung [3, 10] or advanced [11] cancer. Older age, [3] being unemployed, [3] having fewer years of education, [3] not engaging in moderate to strenuous physical activity, [3] having a history of tobacco use, [3, 10] lower performance status, [10] and the presence of pulmonary comorbidity [3, 10] as well as lower pulmonary function test scores, [3, 10] were associated with higher rates of shortness of breath. None of these three studies used a comprehensive list of potential risk factors for shortness of breath in patients receiving chemotherapy. In addition, while data from lung cancer patients suggest that cough and chest tightness are common respiratory symptoms that co-occur with shortness of breath, [12-14] none of the studies cited above [3, 10, 11] evaluated for associations between shortness of breath and other respiratory symptoms in oncology patients receiving chemotherapy.

Shortness of breath is a multidimensional symptom that warrants investigation using the domains of sensory-perceptual experience (i.e., intensity), affective distress, and impact (e.g., QOL). [15] However, as noted in our review, [9] the majority of studies focused primarily on the severity of shortness of breath. In addition, while an evaluation of the overall impact of shortness of breath on oncology patients' physical and psychological functioning is important, [15] no studies have done a comprehensive examination of multiple domains of QOL. This lack of knowledge regarding the multiple dimensions of the symptom experience of shortness of breath in the same sample of oncology patients will be addressed in the current study.

LCA is a person-centered analytic approach that can be used to identify subgroups (i.e., latent classes) of patients with similar symptom profiles. [16] Given the variability in the occurrence rates of shortness of breath among oncology outpatients, the use of LCA may provide insights into modifiable and non-modifiable risk factors that contribute to inter-individual variability in this symptom. [17] Therefore, the purposes of this study, in a sample of oncology outpatients receiving chemotherapy (n=1338), were to: identify subgroups of patients with distinct shortness of breath profiles; evaluate for differences among the subgroups in demographic and clinical characteristics; evaluate for differences in frequency, severity, and distress of shortness of breath; evaluate for differences in the co-occurrence of other common respiratory symptoms; and evaluate for differences in the QOL outcomes.

METHODS

Patients and settings

This study is part of a larger, longitudinal study of the symptom experience of oncology outpatients receiving chemotherapy. [18] Eligible patients were ≥18 years of age; had a diagnosis of breast, gastrointestinal, gynecological, or lung cancer; had received chemotherapy within the preceding four weeks; were scheduled to receive at least two additional cycles of chemotherapy; were able to read, write, and understand English; and gave written informed consent. Patients were recruited from two Comprehensive Cancer Centers, one Veteran's

Affairs hospital, and four community-based oncology programs during their first or second cycle of chemotherapy. The major reason for refusal was being overwhelmed with their cancer treatment.

Study procedures

The study was approved by the Institutional Review Board at each of the study sites. Of the 2234 patients approached and 1343 consented to participate (60.1% response rate). Of these 1343 patients, 1338 rated the occurrence of shortness of breath a total of six times over two chemotherapy cycles (i.e., prior to chemotherapy administration (assessments 1 and 4), approximately 1 week after chemotherapy administration (assessments 2 and 5), and approximately 2 weeks after chemotherapy administration (assessments 3 and 6)). Patients completed the other measures used in this analysis at enrollment (i.e., prior to patients' second or third cycle of chemotherapy).

Instruments

Demographic and Clinical Measures

Patients completed a demographic questionnaire, KPS scale, [19] SCQ, [20] AUDIT, [21] and smoking history questionnaire. Level of exercise was assessed using an investigator developed questionnaire. Based on patients' responses, they were categorized into one of three exercise groups (i.e., no exercise, <150 minutes per week, $\geq$150minutes per week). [22] Medical records were reviewed for disease and treatment information.

Measure of shortness of breath and co-occurring respiratory symptoms

The shortness of breath item from the MSAS was used to assess for the occurrence of shortness of breath at each of the six assessments. Frequency, severity, and distress of shortness of breath were evaluated using data from the enrollment assessment. In addition, the MSAS occurrence rates for chest tightness, difficulty breathing, and cough at enrollment were evaluated. Validity and reliability of the MSAS are well established. [23]

Measures of QOL

Disease-specific and generic measures of QOL were used in this study. Disease-specific QOL was evaluated using the MQOLS-PV. [24] This 41-item instrument measures four domains of QOL (i.e., physical, psychological, social, spiritual well-being) in oncology patients, as well as a total QOL score. The MQOLS-PV has well-established validity and reliability. [25]

The SF-12 was the generic measure of QOL. The SF-12 consists of 12 questions about physical and mental health as well as overall health status. The SF-12 was scored into two components that measure physical (PCS) and psychological (MCS) function. These scores can range from 0 to 100. Higher PCS and MCS scores indicate better physical and psychological functioning, respectively. The SF-12 has well-established validity and reliability. [26]

Data analysis

Descriptive statistics and frequency distributions were generated for sample characteristics at enrollment using the SPSS version 28 (IBM Corporation, Armonk, NY). As was done previously, [27] unconditional LCA was used to identify shortness of breath profiles that characterized unobserved subgroups of patients (i.e., latent classes) over the six assessments. Before performing the LCA, patients who reported the occurrence of shortness of breath for $\leq$1 of the six assessments were identified and labeled as the "None" class (n=943, 70.5%). Then, the LCA was performed on the remaining 395 patients using MPlus™ Version 8.4. [28]

Estimation was carried out with full information maximum likelihood with standard error and a Chi square test that are robust to non-normality and non-independence of observations (“estimator=MLR”). Model fit was evaluated to identify the solution that best characterized the observed latent class structure with the BIC, VLRM, entropy, and latent class percentages that were large enough to be reliable. [29] Missing data were accommodated for with the use of the EM algorithm. [30]

Differences among the latent classes in demographic, clinical, and symptom characteristics, as well as QOL outcomes, were evaluated using parametric and nonparametric

tests. A p-value of <.05 was considered statistically significant. Post hoc contrasts were done using a Bonferroni corrected p-value of <.008 (.05/6 possible pairwise comparisons).

RESULTS

Latent class analysis

The 943 patients (70.5%) who had ≤1 occurrence of shortness of breath over the six assessments were classified as the None class. For the remaining 395 patients whose data were entered into the LCA, a three-class solution was selected because the 3-class solution fit the data better than the 2- and 4 class solutions (detailed in Table 1).

Figure 1 displays the trajectories for the occurrence of shortness of breath among the latent classes. For the decreasing class (8.2%), the occurrence rates for shortness of breath decreased from the first to the fourth assessments; dramatically decreased from the fourth to the fifth assessments; and then increased slightly from the fifth to sixth assessments. For the increasing class (7.8%), the occurrence rates for shortness of breath decreased slightly from the first to second assessments; increased gradually from the second to the fifth assessments; and decreased slightly to the sixth assessment. For the High class (13.5%), the occurrence rates for shortness of breath remained consistently high over the six assessments.

Demographic and clinical characteristics

Compared to the None class, the High class was more likely to live alone, less likely to be employed, and more likely to report a previous or current history of smoking (Table 2). In addition, they were more likely to have multiple cancer treatments, more likely to have lung metastasis, more likely to be receiving chemotherapy on 21- or 28-day cycles, and more likely to self-report a diagnosis of osteoarthritis, back pain, and rheumatoid arthritis. Compared to the None class, the Decreasing and High classes had lower KPS scores, a higher number of comorbidities, higher SCQ scores, and were more likely to self-report a diagnosis of depression. Compared to the None and Decreasing classes, the High class was more likely to be older and more likely to have lung cancer.

In the total sample, compared to the None class, the Decreasing and High classes had lower hemoglobin levels, hematocrit levels, and RBC counts (Table 3). In males, compared to the None and Increasing classes, the Decreasing class had lower hemoglobin levels. Compared to the other three classes, the Decreasing class had lower hematocrit levels. Compared to the None and High classes, the Decreasing class had lower RBC counts. In females, compared to the None class, the High class had lower hemoglobin levels, hematocrit levels, and RBC counts.

Frequency, severity, and distress of shortness of breath

As shown in Figure 2A, for the patients who reported the occurrence of shortness of breath, significant differences were found among the classes in its frequency ($p < .001$). Post-hoc contrasts found that compared with the Decreasing class, the High class reported a higher frequency of shortness of breath. In terms of severity (Figure 2B), significant differences were found among the classes ($p = .006$). Post-hoc contrasts found that compared to the Increasing and Decreasing classes, the High class had more severe shortness of breath. No differences in distress ratings for shortness of breath were found among the classes (Figure 2C).

Co-occurrence of other respiratory symptoms

Compared to the None class, the other three classes reported higher occurrence rates for chest tightness and difficulty breathing (Table 4). Compared to the None class, the Decreasing and High classes reported higher occurrence rates for cough. Compared to the Decreasing class, the Increasing class reported a lower occurrence rate for difficulty breathing. Compared to the Increasing class, the High class reported higher occurrence rates for difficulty breathing and cough.

QOL scores

For the MQOLS-PV, compared to the None class, the Decreasing and High classes had lower scores for psychological and social well-being, and total QOL (Table 5). Compared to the None class, the other three classes had a lower physical well-being score. Compared to the Increasing class, the High class had a lower spiritual well-being and total QOL scores.

For the SF-12, compared to the None class, the Decreasing and High classes had lower role physical, bodily pain, general health, vitality, role emotional, mental health, and MCS scores. Compared to the None class, the other three classes had lower physical and social functioning and PCS scores. Compared to the Increasing class, the High class had lower physical functioning and PCS scores.

DISCUSSION

This study is the first to use LCA to identify subgroups of oncology patients with distinct shortness of breath profiles; evaluate its frequency, severity, and distress; describe the co-occurrence of other respiratory symptoms, and describe the impact of shortness of breath on patients' QOL. Of note, across multiple types of cancer, approximately 30% of our patients reported shortness of breath. While our percentage is lower than the 44.4% reported in patients with advanced cancer receiving outpatient palliative care, [6] these findings suggest that shortness of breath is a significant problem that warrants ongoing assessment and management in patients undergoing active treatment.

For the three classes who reported shortness of breath, the patterns of change in its occurrence were distinct (Figure 1). Of note, the High class had persistently high occurrence rates of shortness of breath for almost two months. In addition, for a larger percentage of patients in this class, their episodes of shortness of breath were more frequent and more severe (Figure 2). In terms of the Decreasing class, while detailed information is not available, a plausible hypothesis for this class' trajectory is that they received effective interventions that decreased their shortness of breath (see below). In terms of the Increasing class, while specific data are not available, the increase in the occurrence rate of shortness of breath may be related to pulmonary toxicities associated with chemotherapy; [7] lack of efficacy of the current treatment; and/or worsening of other chronic conditions.

Demographic characteristics

While not identified as a risk factor in previous studies, [3, 10, 11] compared to the None class, the Increasing and High classes were more likely to report a lower annual household income. In addition, the High class was more likely to be unemployed. Persistent shortness of breath may interfere with one's ability to work or remain employed. [2, 12] These socioeconomic factors may contribute to a delay in seeking care and receiving timely symptom management interventions for shortness of breath.

While not modifiable, older age was a risk factor for being in the High class. Our finding is consistent with a previous report that noted that in a sample of older adults, approximately 30% reported shortness of breath despite the absence of cardiopulmonary comorbidities, obesity, or renal impairment. [31] This association between older age and higher rates of shortness of breath in our sample may be related to vertebral deformities, as well as decreases in lung elasticity and respiratory muscle strength that occur with aging. [32]

Clinical characteristics

Compared to the None class, the Decreasing and High classes were more likely to have a higher number of comorbidities, a higher comorbidity burden, and a poorer functional status. In terms of specific comorbidities, in both of these classes, over 25% of the patients self-reported a diagnosis of depression. This finding is consistent with two studies of patients with lung cancer that used latent variable modeling to create subgroups of patients with distinct profiles using ratings of function [33] and illness perceptions. [34] In both studies, patients with the worst profiles reported higher rates of shortness of breath and depressive symptoms. Equally important, in a study that evaluated the efficacy of antidepressants in patients with advanced cancer, [35] both depression and dyspnea scores decreased over time.

In addition, the High class reported higher rates of osteoarthritis, rheumatoid arthritis, and back pain. Our finding is consistent with a study of community-dwelling older adults that found that individuals with shortness of breath were more likely to experience the co-occurrence

of back pain and arthritis pain. [36] These findings suggest patients who report shortness of breath need to be evaluated for depression and pain and have appropriate symptom management interventions prescribed.

Consistent with previous studies, [3, 10] a larger percentage of patients in the High class were past or current smokers, self-reported lung disease, and had primary or metastatic lung cancer. These risk factors are not surprising given that 56.7% of lung cancer patients at the time of diagnosis [10] and 95% of patients with chronic obstructive pulmonary disease [8] report shortness of breath. In addition, it is well documented that smoking causes or worsens lung disease and lung cancer [37] and that pre-existing lung diseases are associated with an increased risk of lung cancer. [38] Equally important, the co-occurrence of respiratory disease and lung cancer increases the risk of developing drug-induced pulmonary toxicity. [7]

A large number of treatment factors were associated with membership in the High class. Overall, this class was more likely to have received multiple types of cancer treatment and were more likely to be receiving targeted therapy. For the patients in this class who had breast or lung cancer, the receipt of thoracic surgery and/or thoracic or whole breast radiotherapy may damage lung tissue, create scar tissue, and result in pulmonary fibrosis. [39, 40] In addition, the administration of platinum- and/or taxane-containing regimens, that are routinely used to treat lung, breast, gastric, and gynecologic cancers, are associated with pulmonary toxicity. [7, 41] In terms of targeted therapy, of the 392 patients in the total sample who received targeted therapy, 46.2% (n = 181) of them were in the High class. While a detailed analysis of associations between shortness of breath and specific targeted therapies cannot be performed due to the wide variety of agents administered, additional research is warranted to evaluate for differences in the occurrence and severity of this symptom in patients who do and do not receive these agents.

Interestingly, compared to the None class, a higher percentage of patients in the Decreasing class reported anemia (Table 2). In addition, the male patients in this class had

lower hemoglobin levels, hematocrit levels, and RBC counts. This shortness of breath trajectory is somewhat surprising because this symptom is commonly reported by oncology patients with anemia. One potential explanation for the decreases in the occurrence of shortness of breath in this class is that these patients received blood transfusions with a resultant increase in the oxygen carrying capacity of the blood.

Co-occurring respiratory symptoms

Compared to the None class, the other three classes reported higher occurrence rates for chest tightness and difficulty breathing. While the exact etiology for chest tightness is oncology patients is unknown, 17.8% of our total sample of patients with heterogeneous types of cancer reported its occurrence. Our finding is supported by a study of patients with advanced cancer and COPD, [13] that found that chest tightness was a unique symptom that was reported only by the oncology patients.

In terms of difficulty breathing, 19.9% of the total sample reported this symptom at enrollment which is lower than the occurrence rate for shortness of breath (i.e., 26.9% of the total sample at enrollment). While the literature suggests that these two symptoms are distinct, [13, 15] additional research is warranted to determine how patients interpret these two descriptors and whether the risk factors for and mechanisms that underlie these two symptoms are similar. Potential etiologies for the co-occurrence of chest tightness and difficulty breathing with shortness of breath include ongoing irritation of pulmonary afferents from the cancer itself, airway inflammation, and/or a pleural effusion. [15]

While the overall occurrence rate for cough in the total sample was 32.6% at enrollment, compared with the None class, these rates were higher in the Decreasing and High classes. Our finding is consistent with previous reports of cough in 35.1% to 42.9% of oncology outpatients receiving active treatment. [42, 43] While the exact etiologies for cough are not well understood, they may include: activation of bronchopulmonary C-fibers by the cancer itself, a pleural effusion, and/or toxicities of cancer treatments. [44] Given the relatively high co-

occurrence rates for all four symptoms, they should be routinely assessed as a “bundle” in patients who report any singular symptom.

QOL outcomes

In terms of QOL outcomes, it should be noted that for the SF-12, all four classes reported PCS and MCS scores of below 50, which is normative score for the general population of the United States. [26] Compared to the None class, both the Decreasing and High classes reported worse scores for the QOL domains of physical, psychological, and social functioning on both the general and cancer-specific measures. Our findings are consistent with a study of patients with lung cancer who were scheduled for chemotherapy that reported that shortness of breath resulted in significant impairments in daily activities. [45] In addition, shortness of breath may deter patients from participating in social activities which can increase feelings of social isolation. [2]

LIMITATIONS

Several limitations warrant consideration. Given that our sample was relatively homogenous in terms of gender and ethnicity, our findings may not generalize to more diverse racial and ethnic groups. While this study used a valid and reliable measure to assess the subjective experience of shortness of breath, future studies need to evaluate for correlations objective measures of pulmonary function. In addition, detailed information is needed on the patients’ specific cardiopulmonary conditions. Finally, information on the pharmacologic and nonpharmacologic treatments for shortness of breath were not available for our sample.

CONCLUSIONS

Despite these limitations, this study provides new information on the occurrence severity, distress, and risk factors for shortness of breath, co-occurring respiratory symptoms, and QOL outcomes in a sample of patients with heterogeneous types of cancer. In addition, a number of modifiable (e.g., poorer physical functioning, occurrence of anemia and depression) risk factors were identified. If identified as causative factors, both anemia and depression can be treated. It

should be noted that in two studies that evaluated the efficacy of pulmonary rehabilitation to improve physical functioning, shortness of breath, and QOL in patients with lung cancer receiving chemotherapy, [46, 47] patients who received the intervention showed decreases in the severity of shortness of breath and improvements in physical function. Given these studies positive results, oncology clinicians can recommend this type of program to decrease shortness of breath during chemotherapy.

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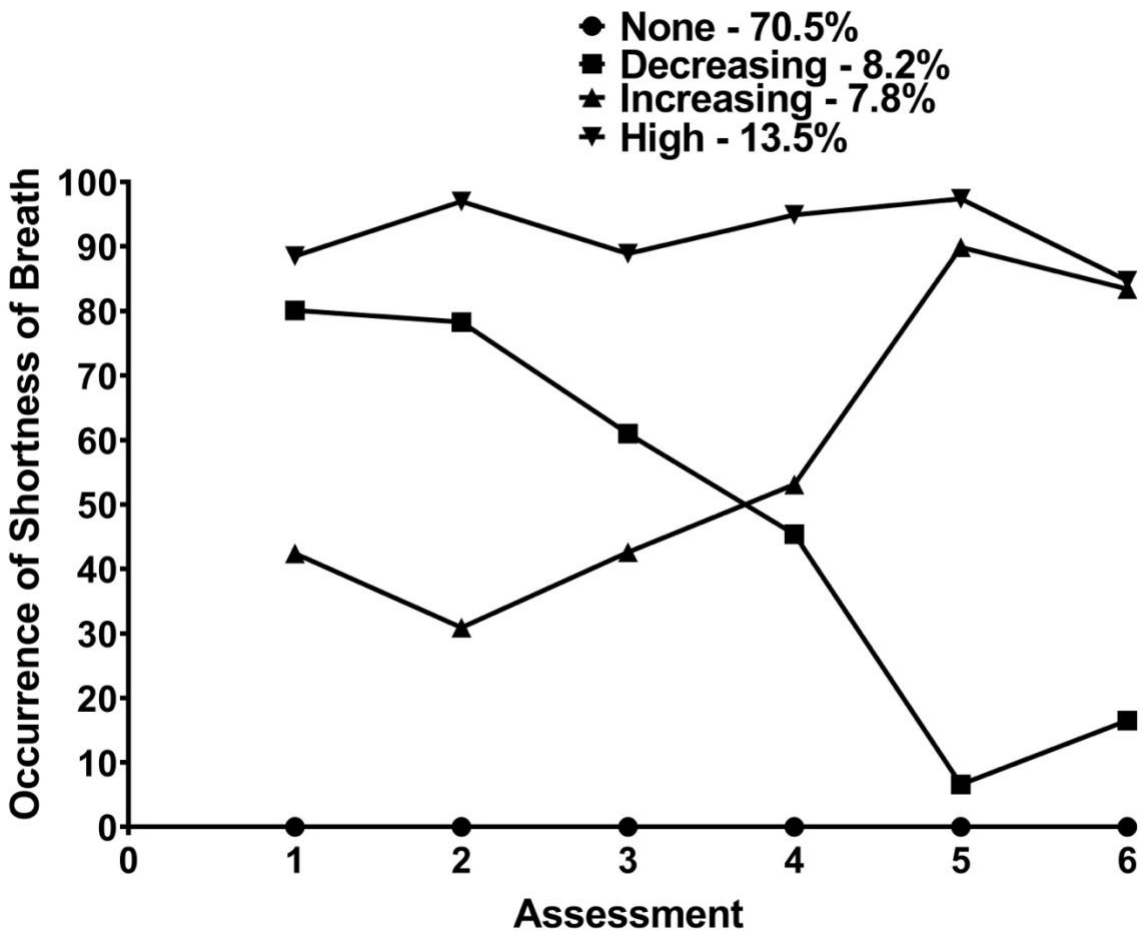

Figure 4.1. Trajectories of shortness of breath occurrence for the four latent class

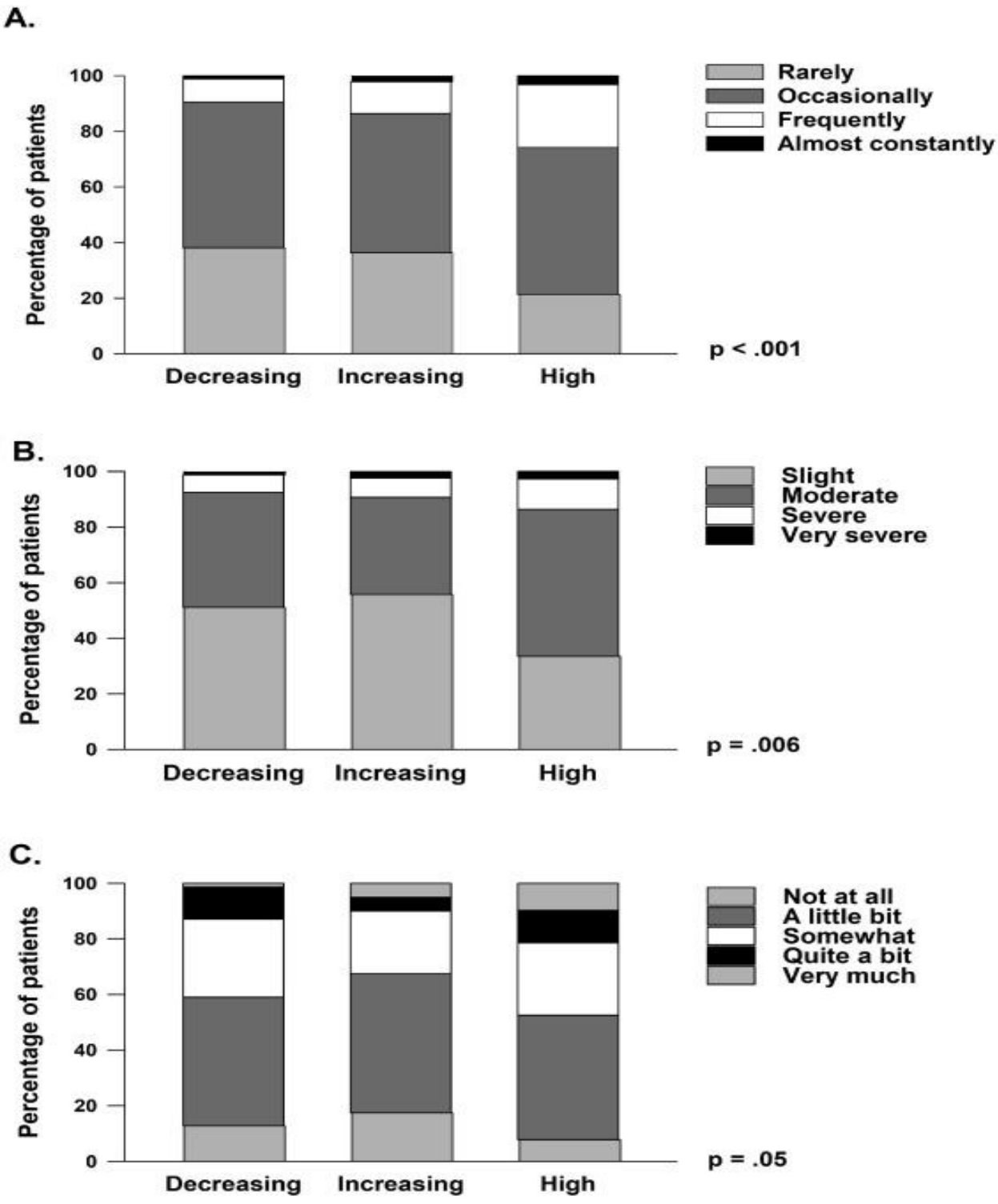

Figure 4.2. Percentages of patients in the decreasing, increasing, and high classes who rated the frequency (a), severity (b), and distress (c) associated with shortness of breath

Table 4.1. Shortness of Breath Occurrence Latent Class Solutions and Fit Indices for One through Four Classes

Model	LL	AIC	BIC	Entropy	VLMR
1 Class	-1325.86	2663.72	2687.60	n/a	n/a
2 Class	-1262.46	2550.93	2602.65	0.66	126.80[+]
3 Class [a]	-1210.75	2461.50	2541.08	0.66	103.43[‡]
4 Class	-1204.76	2463.51	2570.94	0.73	Ns

Baseline entropy and VLMR are not applicable for the one-class solution

[+]p = .0001; [‡]p < .00005

[a] The 3-class solution was selected because the BIC for that solution was lower than the BIC for the 2-class solution. In addition, the VLMR was significant for the 3-class solution, indicating that three classes fit the data better than two classes. The BIC increased for the 4-class compared to the 3-class solution, indicating that the fit of the 4-class solution was worse. Further, the VLMR was not significant for the 4-class solution, indicating that too many classes had been extracted.

Abbreviations: AIC = Akaike's Information Criterion; BIC = Bayesian Information Criterion; LL = log-likelihood; n/a = not applicable; ns = not significant, VLMR = Vuong-Lo-Mendell-Rubin likelihood ratio test for the K vs. K-1 model

Table 4.2. Differences in Demographic and Clinical Characteristics at Enrollment Among the Shortness of Breath Latent Classes

Characteristic	None (0) 70.5% (n=943)	Decreasing (1) 8.2% (n=109)	Increasing (2) 7.8% (n=105)	High (3) 13.5% (n=181)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	57.0 (12.3)	55.3 (13.0)	56.5 (12.2)	59.6 (12.0)	F = 3.44, p = .016 0 and 1 < 3
Education (years)	16.3 (3.0)	15.8 (2.8)	16.1 (3.0)	16.2 (3.1)	F = 0.69, p = .558
Body mass index (kilogram/meter squared)	25.9 (5.4)	26.2 (6.4)	27.4 (6.5)	26.8 (6.0)	F = 3.05, p = .028 no significant pairwise contrasts
Alcohol Use Disorders Identification Test score	3.1 (2.5)	2.9 (2.3)	2.5 (2.5)	2.8 (2.5)	F = 1.11, p = .346
Karnofsky Performance Status score	81.7 (12.0)	75.4 (12.4)	78.9 (12.9)	74.7 (12.7)	F = 21.31, p <.001 0 > 1 and 3, 2 > 3
Number of comorbid conditions	2.2 (1.3)	2.7 (1.6)	2.5 (1.5)	3.1 (1.6)	F = 21.05, p <.001 0 < 1 and 3, 2 < 3
Self-administered Comorbidity Questionnaire score	5.1 (2.8)	6.2 (3.5)	5.8 (3.6)	7.1 (4.0)	F = 24.27, p <.001 0 < 1 and 3, 2 < 3
Time since diagnosis (years)	1.7 (3.2)	2.7 (5.5)	2.3 (4.0)	2.8 (5.3)	KW = 10.42, p = .015 no significant pairwise contrasts
Time since diagnosis (years, median)	0.41	0.50	0.44	0.51	
Number of prior cancer treatments	1.5 (1.4)	1.9 (1.7)	1.7 (1.5)	1.8 (1.7)	F = 4.27, p = .005 0 < 3
Number of metastatic sites including lymph node involvement[a]	1.2 (1.2)	1.2 (1.2)	1.3 (1.2)	1.4 (1.4)	F = 1.06, p = .365
Number of metastatic sites excluding lymph node involvement	0.8 (1.0)	0.8 (1.0)	0.8 (1.1)	1.0 (1.2)	F = 1.84, p = .138

Table 4.2. Differences in Demographic and Clinical Characteristics at Enrollment Among the Shortness of Breath Latent Classes

Characteristic	None (0) 70.5% (n=943)	Decreasing (1) 8.2% (n=109)	Increasing (2) 7.8% (n=105)	High (3) 13.5% (n=181)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
MAX2 score	0.17 (0.08)	0.17 (0.08)	0.18 (0.08)	0.18 (0.09)	F = 0.60, p = .613
	% (n)	% (n)	% (n)	% (n)	
Gender (% female)	75.2 (708)	89.0 (97)	84.8 (89)	80.7 (146)	X^2 = 15.51, p = .001 0 < 1
Self-reported ethnicity White Asian or Pacific Islander Black Hispanic, Mixed, or Other	 69.6 (649) 13.2 (123) 6.6 (62) 10.6 (99)	 61.7 (66) 14.0 (15) 12.1 (13) 12.1 (13)	 67.0 (69) 13.6 (14) 7.8 (8) 11.7 (12)	 76.4 (136) 7.3 (13) 6.7 (12) 9.6 (17)	X^2 = 11.41, p = .249
Married or partnered (% yes)	67.0 (623)	62.6 (67)	52.9 (54)	58.9 (106)	X^2 = 11.10, p = .011 0 > 2
Lives alone (% yes)	19.7 (183)	17.6 (19)	30.1 (31)	28.5 (51)	X^2 = 12.50, p = .006 0 < 3
Currently employed (% yes)	37.3 (348)	30.6 (33)	34.6 (36)	26.7 (48)	X^2 = 8.66, p = .034 0 > 3
Annual household income Less than $30,000$^+$ $30,000 to $70,000 $70,000 to $100,000 Greater than $100,000	 14.8 (125) 21.2 (179) 17.4 (147) 46.6 (394)	 28.9 (28) 18.6 (18) 14.4 (14) 38.1 (37)	 26.4 (24) 24.2 (22) 13.2 (12) 36.3 (33)	 26.1 (43) 20.0 (33) 18.2 (30) 35.8 (59)	KW = 19.53, p <.001 0 > 2 and 3
Child care responsibilities (% yes)	22.8 (211)	22.9 (24)	22.8 (23)	18.2 (32)	X^2 = 1.86, p = .602
Elder care responsibilities (% yes)	7.4 (64)	7.4 (7)	14.1 (14)	7.0 (11)	X^2 = 5.78, p = .123
Past or current history of smoking (% yes)	32.9 (306)	37.0 (40)	37.6 (38)	45.5 (81)	X^2 = 10.76, p = .013 0 < 3

Table 4.2. Differences in Demographic and Clinical Characteristics at Enrollment Among the Shortness of Breath Latent Classes

Characteristic	None (0) 70.5% (n=943)	Decreasing (1) 8.2% (n=109)	Increasing (2) 7.8% (n=105)	High (3) 13.5% (n=181)	Statistics
	% (n)	% (n)	% (n)	% (n)	
Level of exercise					$X^2 = 7.66$, p = .264
Does not exercise on a regular basis	35.1 (251)	40.9 (36)	39.2 (31)	43.5 (64)	
Exercises less than 150 minutes per week	45.1 (323)	35.2 (31)	44.3 (35)	41.5 (61)	
Exercises 150 or more minutes per week	19.8 (142)	23.9 (21)	16.5 (13)	15.0 (22)	
Specific comorbid conditions (% yes)					
Heart disease	5.1 (48)	6.4 (7)	3.8 (4)	9.9 (18)	$X^2 = 7.45$, p = .059
High blood pressure	30.1 (284)	32.1 (35)	25.7 (27)	32.6 (59)	$X^2 = 1.68$, p = .641
Lung disease	7.5 (71)	14.7 (16)	10.5 (11)	29.3 (53)	$X^2 = 73.16$, p <.001 0, 1, & 2 < 3
Diabetes	8.2 (77)	15.6 (17)	7.6 (8)	10.5 (19)	$X^2 = 7.30$, p= .063
Ulcer or stomach disease	4.5 (42)	5.5 (6)	4.8 (5)	6.6 (12)	$X^2 = 1.66$, p = .645
Kidney disease	1.1 (10)	1.8 (2)	1.0 (1)	3.3 (6)	$X^2 = 5.81$, p = .121
Liver disease	6.0 (57)	5.5 (6)	9.5 (10)	7.2 (13)	$X^2 = 2.23$, p = .526
Anemia or blood disease	10.3 (97)	19.3 (21)	18.1 (19)	14.9 (27)	$X^2 = 12.90$, p= .005 0 < 1
Depression	15.4 (145)	27.5 (30)	22.9 (24)	32.0 (58)	$X^2 = 33.90$, p <.001 0 < 1 and 3
Osteoarthritis	10.4 (98)	11.9 (13)	16.2 (17)	19.3 (35)	$X^2 = 13.07$, p = .004 0 < 3
Back pain	22.2 (209)	33.0 (36)	31.4 (33)	36.5 (66)	$X^2 = 22.02$, p <.001 0 < 3
Rheumatoid arthritis	2.9 (27)	1.8 (2)	1.0 (1)	7.2 (13)	$X^2 = 11.93$, p = .008 0 < 3

Table 4.2. Differences in Demographic and Clinical Characteristics at Enrollment Among the Shortness of Breath Latent Classes

Characteristic	None (0) 70.5% (n=943)	Decreasing (1) 8.2% (n=109)	Increasing (2) 7.8% (n=105)	High (3) 13.5% (n=181)	Statistics
	% (n)	% (n)	% (n)	% (n)	
Cancer diagnosis					X^2 = 76.19, p <.001
Breast cancer	38.4 (362)	51.4 (56)	46.7 (49)	39.8 (72)	NS
Gastrointestinal cancer	35.4 (334)	21.1 (23)	21.0 (22)	16.6 (30)	0 > 1, 2, & 3
Gynecological cancer	17.7 (167)	15.6 (17)	18.1 (19)	16.6 (30)	NS
Lung cancer	8.5 (80)	11.9 (13)	14.3 (15)	27.1 (49)	0 and 1 < 3
Co-occurrence of lung cancer and lung disease	56.3 (45)	61.5 (8)	40.0 (6)	79.6 (39)	X^2 = 10.68, p = .014 0 and 2 < 3
Prior cancer treatment					X^2 = 26.42, p = .002
No prior treatment	25.6 (235)	19.8 (21)	18.8 (19)	28.2 (50)	NS
Only surgery, CTX, or RT	43.6 (400)	41.5 (44)	46.5 (47)	31.6 (56)	0 > 3
Surgery and CTX, or surgery and RT, or CTX and RT	20.2 (185)	20.8 (22)	17.8 (18)	18.6 (33)	NS
Surgery and CTX and RT	10.6 (97)	17.9 (19)	16.8 (17)	21.5 (38)	0 < 3
Receipt of targeted therapy (% yes)	27.2 (251)	33.3 (36)	31.7 (33)	40.9 (72)	X^2 = 14.18, p = .003 0 < 3
Cycle length					
14 day cycle+	45.5 (425)	40.7 (44)	41.0 (43)	25.8 (46)	KW = 24.14, p <.001 0 < 3
21 day cycle	48.0 (449)	52.8 (57)	49.5 (52)	63.5 (113)	
28 day cycle	6.5 (61)	6.5 (7)	9.5 (10)	10.7 (19)	
Metastatic sites					
No metastasis	32.2 (299)	34.0 (36)	30.8 (32)	33.3 (60)	
Only lymph node metastasis	23.2 (216)	17.9 (19)	26.0 (27)	16.1 (29)	
Only metastatic disease in other sites	21.1 (196)	20.8 (22)	19.2 (20)	22.8 (41)	X^2 = 7.15, p = .622
Metastatic disease in lymph nodes and other sites	23.5 (219)	27.4 (29)	24.0 (25)	27.8 (50)	
Lung metastasis (% yes)	14.1 (89)	21.1 (15)	15.1 (11)	30.0 (36)	X^2 = 19.28, p <.001 0 < 3

Table 4.2. Differences in Demographic and Clinical Characteristics at Enrollment Among the Shortness of Breath Latent Classes

Characteristic	None (0) 70.5% (n=943)	Decreasing (1) 8.2% (n=109)	Increasing (2) 7.8% (n=105)	High (3) 13.5% (n=181)	Statistics
	% (n)	% (n)	% (n)	% (n)	
Emetogenicity of the CTX regimen					KW = 3.41, p = .332
Minimal/low	18.1 (169)	24.8 (27)	19.0 (20)	24.2 (43)	
Moderate	63.2 (591)	50.5 (55)	56.2 (59)	59.0 (105)	
High	18.7 (175)	24.8 (27)	24.8 (26)	16.9 (30)	
Antiemetic regimen					X^2 = 4.02, p = .910
None	7.2 (66)	7.6 (8)	5.9 (6)	6.9 (12)	
Steroid alone or serotonin receptor antagonist alone	19.5 (178)	22.9 (24)	23.5 (24)	22.3 (39)	
Serotonin receptor antagonist and steroid	49.0 (448)	41.0 (43)	46.1 (47)	45.7 (80)	
NK-1 receptor antagonist and two other antiemetics	24.3 (222)	28.6 (30)	24.5 (25)	25.1 (44)	

[a]Total number of metastatic sites evaluated was 9.
[+]Reference group

Abbreviations: CTX = chemotherapy, KW = Kruskal Wallis, NK-1 = neurokinin-1, NS = not significant, RT = radiation therapy, SD = standard deviation

Table 4.3. Total Sample and Within Gender Differences in Red Blood Cell Counts, Hemoglobin Levels, and Hematocrit Levels Among the Shortness of Breath Latent Classes

Total Sample					
Blood test	None (0) 70.5% (n=943)	Decreasing (1) 8.2% (n=109)	Increasing (2) 7.8% (n=105)	High (3) 13.5% (n=181)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Hemoglobin (grams/deciliter)	11.7 (1.4)	11.0 (1.4)	11.4 (1.4)	11.3 (1.4)	KW = 24.50, p<.001 0 > 1 and 3
Hematocrit (%)	34.9 (4.1)	33.1 (4.1)	34.0 (4.1)	33.8 (4.2)	KW = 26.09, p<.001 0 > 1 and 3
RBC count (x10^6 microliters)	3.9 (0.5)	3.7 (0.6)	3.7 (0.5)	3.7 (0.6)	KW = 21.36, p<.001 0 > 1 and 3
Males					
Blood test	None (0) 78.8% (n=234)	Decreasing (1) 4.0% (n=12)	Increasing (2) 5.4% (n=16)	High (3) 11.8% (n=35)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Hemoglobin (13.8 to 17.2 grams/deciliter)	12.3 (1.6)	10.3 (1.7)	12.3 (1.3)	11.9 (1.8)	KW = 13.71, p=.003 1 < 0 and 2
Hematocrit (41% to 50%)	36.8 (4.4)	30.9 (4.4)	36.6 (3.4)	36.0 (5.5)	KW = 15.17, p=.002 1 < 0, 2, and 3
RBC count (4.7 to 6.1 x10^6 microliters)	4.1 (0.6)	3.3 (0.5)	4.0 (0.4)	4.0 (0.7)	KW = 16.63, p<.001 1 < 0 and 3
Females					
Blood test	None (0) 68.1% (n=708)	Decreasing (1) 9.3% (n=97)	Increasing (2) 8.6% (n=89)	High (3) 14.0% (n=146)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Hemoglobin (12.1 to 15.1 grams/deciliter)	11.5 (1.3)	11.1 (1.3)	11.2 (1.4)	11.1 (1.2)	KW = 11.63, p=.009 0 > 3
Hematocrit (36% to 48%)	34.3 (3.7)	33.4 (4.0)	33.6 (4.1)	33.3 (3.7)	KW = 12.58, p=.006 0 > 3
RBC count (4.2 to 5.4 x10^6 microliters)	3.8 (0.5)	3.7 (0.6)	3.7 (0.5)	3.6 (0.5)	KW = 12.76, p=.005 0 > 3

Abbreviations: KW = Kruskal Wallis, RBC = red blood cell, SD = standard deviation

Normal values for males and female are in parentheses

Table 4.4. Differences in the Occurrence of Respiratory Symptoms Among the Shortness of Breath Latent Classes

Symptom	**None (0) 70.5% (n=943)**	**Decreasing (1) 8.2% (n=109)**	**Increasing (2) 7.9% (n=105)**	**High (3) 13.5% (n=181)**	**Statistics**
	% (n)	% (n)	% (n)	% (n)	
Chest tightness	10.9 (102)	42.2 (46)	25.7 (27)	34.6 (62)	$X^2 = 113.85$, p <.001 0 < 1, 2, and 3
Difficulty breathing	7.5 (70)	50.5 (55)	24.8 (26)	63.7 (114)	$X^2 = 370.77$, p <.001 0 < 1, 2, and 3; 1 > 2; 2 < 3
Cough	26.5 (248)	46.8 (51)	36.2 (38)	53.6 (96)	$X^2 = 62.53$, p <.001 0 < 1 and 3; 2 < 3

Table 4.5. Differences in Quality of Life Outcomes Among the Shortness of Breath Latent Classes

QOL outcomes	None (0) 70.5% (n=943)	Decreasing (1) 8.2% (n=109)	Increasing (2) 7.9% (n=105)	High (3) 13.5% (n=181)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Multidimensional Quality of Life Scale – Cancer					
Physical well-being	6.9 (1.7)	6.0 (1.8)	6.4 (1.8)	5.8 (1.8)	F = 23.05, p <.001 0 > 1, 2 and 3
Psychological well-being	5.7 (1.8)	4.8 (1.8)	5.4 (1.9)	4.9 (1.8)	F = 15.58, p <.001 0 > 1 and 3
Social well-being	6.0 (2.0)	5.0 (1.9)	5.6 (2.0)	5.0 (2.0)	F = 16.70, p <.001 0 > 1 and 3
Spiritual well-being	5.5 (2.1)	5.6 (2.1)	5.7 (2.0)	5.0 (2.1)	F = 3.11, p =.026 2 > 3
Total QOL score	5.9 (1.4)	5.2 (1.4)	5.7 (1.4)	5.1 (1.4)	F = 23.27, p <.001 0 > 1 and 3; 2 > 3
Medical Outcomes Study Short Form – 12 (SF-12)					
Physical functioning	58.0 (34.0)	40.3 (31.8)	48.0 (35.7)	33.3 (27.7)	F = 33.01, p <.001 0 > 1, 2, and 3; 2 > 3
Role physical	56.0 (28.7)	44.6 (28.7)	48.6 (29.7)	39.6 (28.7)	F = 19.56, p <.001 0 > 1 and 3
Bodily pain	79.1 (26.3)	67.8 (32.6)	72.8 (30.9)	64.1 (30.9)	F = 17.82, p <.001 0 > 1 and 3
General health	66.2 (26.5)	52.2 (29.2)	59.9 (30.4)	51.8 (29.2)	F = 19.78, p <.001 0 > 1 and 3
Vitality	48.6 (26.6)	38.3 (26.5)	41.7 (26.7)	35.0 (25.3)	F = 16.76, p <.001 0 > 1 and 3
Social functioning	70.7 (29.2)	58.6 (32.4)	60.4 (31.8)	56.4 (32.4)	F = 16.22, p <.001 0 > 1, 2, and 3
Role emotional	78.0 (26.6)	69.2 (28.3)	75.2 (26.3)	67.6 (29.4)	F = 9.56, p <.001 0 > 1 and 3
Mental health	73.6 (19.8)	65.0 (23.1)	70.9 (22.5)	67.7 (22.1)	F = 8.61, p <.001 0 > 1 and 3
Physical component summary score	43.0 (10.0)	37.8 (10.4)	39.5 (11.6)	35.2 (10.2)	F = 32.32, p <.001 0 > 1, 2, and 3; 2 > 3
Mental component summary score	49.7 (10.1)	46.6 (11.2)	48.0 (10.2)	47.1 (11.7)	F = 5.37, p =.001 0 > 1 and 3

Abbreviations: QOL = quality of life, SD = standard deviation

Table 4.6. Characteristics Associated with Membership in the Decreasing, Increasing, and High Shortness of Breath Classes

Characteristic[a]	Decreasing	Increasing	High
Demographic Characteristics			
More likely to be older			■
More likely to be female	■		
Less likely to be married/partnered		■	
More likely to live alone			■
Less likely to be employed			■
More likely to have a lower annual income		■	■
Clinical Characteristics			
More likely to have past or current history of smoking			■
Lower functional status	■		■
Higher number of comorbidities	■		■
Higher comorbidity burden	■		■
More likely to self-report lung disease			■
More likely to self-report anemia	■		
More likely to self-report depression	■		■
More likely to self-report osteoarthritis			■
More likely to self-report back pain			■
More likely to self-report rheumatoid arthritis			■
Less likely to have gastrointestinal cancer	■	■	■
More likely to have lung cancer			■
More likely to have lung metastasis			■
More likely to have co-occurrence of lung cancer and lung disease			■
Higher number of cancer treatments			■
Less likely to have received only surgery, CTX, or RT			■
More likely to have received all of the following treatments surgery, radiation, and CTX			■
More likely to be receiving targeted therapy			■
More likely to be receiving CTX on a 21- or 28-day cycle			■
Co-occurrence of Respiratory Symptoms			
More likely to have chest tightness	■	■	■
More likely to have difficulty breathing	■	■	■
More likely to have cough	■		■
QOL outcomes			
Multidimensional QOL Scale – Patient Version			
Lower physical well-being	■	■	■
Lower psychological well-being	■		■
Lower social well-being	■		■
Lower total QOL score	■		■
Medical Outcomes Study – Short Form 12			
Lower physical functioning	■	■	■
Lower role physical	■		■
Lower bodily pain	■		■
Lower general health	■		■
Lower vitality	■		■
Lower social functioning	■	■	■
Lower role emotional	■		■
Lower mental health	■		■
Physical component summary score	■	■	■

Table 4.6. Characteristics Associated with Membership in the Decreasing, Increasing, and High Shortness of Breath Classes

Characteristic[a]	Decreasing	Increasing	High
Mental component summary score	■		■

[a]Comparisons done with the None group
■ – indicates that the class had this characteristic compared to the None class

Abbreviations: CTX = chemotherapy, RBC = red blood cell, RT = radiation therapy, QOL = quality of life

Chapter 5

Higher Lifetime Stress and Symptom Burden Contribute to the Occurrence of Shortness of Breath

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ABSTRACT

Objectives: Among four classes of patients with distinct shortness of breath profiles, evaluate for differences in levels of global, cancer-specific, and cumulative life stress, as well as resilience; evaluate for differences in the occurrence rates for various stressful life events, and evaluate for differences in the severity of common co-occurring symptoms.

Data Sources: Outpatients (n=1338) completed questionnaires six times over two cycles of chemotherapy. The occurrence of shortness of breath was assessed using the Memorial Symptom Assessment Scale. Latent class analysis was used to identify subgroups of patients with distinct shortness of breath profiles. Differences among the classes were evaluated using parametric and nonparametric tests.

Conclusion: Shortness of breath classes were labeled based on their distinct occurrence trajectories: None (70.5%), Decreasing (8.2%), Increasing (7.8%), and High (13.5%). Compared to None class, Decreasing and High classes had higher global and cancer-specific stress scores. The High class reported higher occurrence rates for several adverse childhood experiences. Compared to None class, Decreasing and High classes had higher depression, anxiety, and morning fatigue scores and lower morning energy and cognitive function scores.

Implications for Nursing Practice: Given the additive or synergistic relationships between stress, co-occurring symptoms, and shortness of breath, multimodal interventions that include stress management, exercise training, and/or symptom management may decrease shortness of breath in oncology patients.

Keywords: adverse childhood experiences; cancer; depression; post-traumatic stress disorder; resilience; shortness of breath; stress

INTRODUCTION

The 10% to 70% occurrence rate for shortness of breath in oncology patients provides evidence of the large amount of inter-individual variability in this symptom. [1] However, limited information is available on factors that contribute to this variability. [2] Therefore, effective management of shortness of breath is extremely challenging. [3] Unrelieved shortness of breath is associated with decreases in functional status and quality of life, [4] as well as overall survival. [5]

Given the paucity of research on risk factors for shortness of breath in oncology patients, our team developed the Multifactorial Model of Dyspnea in Patients with Cancer. [6] The six factors included in this model are based on a synthesis of nineteen studies on the occurrence [7-9] and severity [4, 10-24] of dyspnea in oncology patients. The specific factors in this Model include: person (i.e., age, gender, socioeconomic status), clinical (i.e., smoking, respiratory disease, heart disease), and cancer-related (e.g., lung cancer, cancer treatments, anemia) factors, as well as respiratory muscle weakness, co-occurring symptoms (e.g., anxiety, depression, fatigue), and stress. Given that the majority of the studies that provided the foundation for our Model evaluated patients with lung cancer, additional research is warranted on risk factors for shortness of breath in patients with heterogeneous types of cancer undergoing chemotherapy.

LCA is a person-centered analytic approach that can be used to identify modifiable and non-modifiable risk factors associated with subgroups (i.e., latent classes) of patients with distinct symptom profiles. [25] Using this analytic approach, we evaluated for subgroups of patients with distinct shortness of breath profiles. [26] In brief, in a sample of 1338 patients undergoing chemotherapy, 70.5% did not report shortness of breath. Of the remaining 395 patients, three distinct shortness of breath profiles were identified (i.e., Decreasing (8.2%), Increasing (7.8%), and High (13.5%)). Consistent with our conceptual model, risk factors for membership in the High class included: older age, being unemployed, having a history of

smoking, reporting a diagnosis of lung disease, having lung cancer, and having received a higher number of cancer treatments.

While this study provides new information on various demographic and clinical characteristics associated with the occurrence of shortness of breath in patients with heterogeneous types of cancer receiving chemotherapy, [26] differences in the severity of other common co-occurring symptoms and various types of stress and resilience among the classes were not evaluated. As noted in our recent systematic review, [2] studies on the associations between dyspnea and co-occurring symptoms in oncology patients are extremely limited. In addition, despite the growing body of evidence on the role of stress in oncology patients' symptom experiences, [27-29] no studies were identified that evaluated for associations between shortness of breath and stress. [2]

Existing evidence suggests that the hypothalamus is involved in the regulation of respiration under stress. [30, 31] In one cross-sectional study of patients with chronic shortness of breath, [32] higher levels of perceived stress were associated with more severe shortness of breath. In addition, moderate to severe shortness of breath in these patients was associated with flatter diurnal cortisol slopes. [32] While these findings suggest that chronic moderate to severe shortness of breath causes HPA axis dysregulation, additional studies are warranted because only 26.5% of these patients had cancer.

A cancer diagnosis and subsequent treatment(s) are significant SLEs. [33] As noted in one review, [34] 7.3% to 13.8% of oncology patients meet the criteria for PTSD and an additional 10% to 20% meet the criteria for subsyndromal PTSD. These data suggest that cancer-specific SLEs have additive effects on the HPA axis that may impact the perception of dyspnea. While no studies examined the association between shortness of breath and cancer-specific stress, in a study of patients with COPD, [35] positive correlations were found between the severity of shortness of breath and measures of perceived stress and fear of COVID-19.

On the other hand, resilience corresponds to an individual's protective attributes that promote successful adaptation to stressors. [36] In one study of patients with non-small cell lung cancer, [37] individuals with a lower functional status were more likely to have severe dyspnea and lower resilience. In another study of patients with COPD, [38] higher levels of dyspnea were associated with lower levels of resilience. Equally important, a growing body of evidence suggests that early life stress plays a crucial role in shaping an individual's adaptive and maladaptive responses to a variety of stressors in adulthood. [31] Therefore, additional studies are warranted that evaluate for associations between dyspnea and various types of stress (i.e., global, cancer-specific, cumulative life stress) and resilience in the same sample of oncology patients.

Of note, common symptoms (e.g., anxiety, sleep disturbance) experienced by oncology patients may co-occur with shortness of breath. For example, higher levels of anxiety and depression were associated with more severe dyspnea in oncology patients. [9, 11, 15, 24, 39-46] However, among these studies, only four [9, 15, 24, 39] included patients with heterogeneous types of cancer; none evaluated both trait and state anxiety; and the majority of the analyses were limited to correlation coefficients. [15, 39, 41, 43-46]

While less well studied, fatigue is another symptom that demonstrates a positive relationship with dyspnea. [15, 16, 39, 42, 44] In addition, in four studies, [11, 21, 24, 42] positive associations were found between dyspnea and pain. Of note, in two studies of patients with advanced cancer, [15, 39] dyspnea was positively correlated with sleep disturbance. Finally, cognitive impairment is a common symptom in patients undergoing chemotherapy. [47] However, while a positive association was reported between dyspnea and mild cognitive impairment in patients with COPD, asthma, or heart failure, [48] no studies have evaluated this association in oncology patients.

Given the paucity of research on the associations between the occurrence of dyspnea and stress and other common symptoms in oncology patients, the purpose of this study was to

extend our previous findings that identified subgroups of patients with distinct shortness of breath profiles [26] evaluate for differences in levels of global, cancer-specific, and cumulative life stress, as well as resilience among the four shortness of breath classes. In addition, differences among the four classes in the occurrence rates for various SLEs and the severity of common co-occurring symptoms were evaluated.

METHODS

Patients and settings

This study is part of a larger, longitudinal study of the symptom experience of oncology outpatients receiving chemotherapy. [49] Eligible patients were ≥18 years of age; had a diagnosis of breast, gastrointestinal, gynecological, or lung cancer; had received chemotherapy within the preceding four weeks; were scheduled to receive at least two additional cycles of chemotherapy; were able to read, write, and understand English; and gave written informed consent. Patients were recruited from two Comprehensive Cancer Centers, one Veteran's Affairs hospital, and four community-based oncology programs during their first or second cycle of chemotherapy. The major reason for refusal was being overwhelmed with their cancer treatment.

Study procedures

Study was approved by the Committee on Human Research at the University of California, San Francisco and by the Institutional Review Board at each of the study sites. Written informed consent was obtained from all patients. Patients completed the shortness of breath measure, a total of six times over two cycles of chemotherapy. Stress and symptom measures were completed at enrollment (i.e., prior to the second or third cycle of chemotherapy). Medical records were reviewed for disease and treatment information.

Instruments

Demographic and Clinical Measures

Patients completed a demographic questionnaire, KPS scale, [50] SCQ, [51] AUDIT, [52] and smoking history questionnaire. Level of exercise was assessed using an investigator developed questionnaire. Using the recommendation for physical activity from the Office of Disease Prevention and Health Promotion's Healthy People 2020 report, [53] patients' responses were categorized into one of three exercise groups (i.e., no exercise, <150 minutes per week, ≥150minutes per week). [54] Medical records were reviewed for disease and treatment information.

Measure of Shortness of Breath

The shortness of breath item from the MSAS was used to assess for the occurrence of shortness of breath (i.e., yes or no) at each of the six assessments. Validity and reliability of the MSAS are well established. [55]

Stress and Resilience Measures

The 14-item PSS was used as a measure of global perceived stress according to the degree that life circumstances are appraised as stressful over the course of the previous week. [56] Each item was rated on a 0 to 4 Likert scale (i.e., 0 = never, 1 = almost never, 2 = sometimes, 3 = fairly often, 4 = very often). Total PSS scores can range from 0 to 56. Its Cronbach's alpha was 0.89.

The 22-item IES-R was used to measure cancer-related distress. [57, 58] Patients rated each item based on how distressing each potential difficulty was for them during the past week "with respect to their cancer and its treatment." Each item was rated on a 0 (not at all) to 4 (extremely) Likert scale. Three subscales evaluate levels of intrusion, avoidance, and hyperarousal perceived by the patient. The total score can range from 0 to 88. Sum scores of ≥24 indicate clinically meaningful post-traumatic symptomatology and scores of ≥33 indicate probable PTSD. [59] Cronbach's alpha for the IES-R total score was 0.92.

The 30-item LSC-R is an index of lifetime trauma exposure (e.g., being mugged, sexual assault). [60] The total LSC–R score is obtained by summing the total number of events endorsed (range of 0 to 30). If the patient endorsed an event, the patient was asked to indicate how much that stressor affected their life in the past year, from 1 (not at all) to 5 (extremely). These responses were summed to yield a total “affected” sum score. In addition, a PTSD sum score was created based on the number of positively endorsed items (out of 21) that reflect the DSM-IV PTSD Criteria A for having experienced a traumatic event.

The 10-item CDRS evaluates a patient’s personal ability to handle adversity (e.g., “I am able to adapt when changes occur”). [61, 62] Items are scored on a 5-point Likert scale (“not true at all” to “true nearly all of the time”). Total scores range from 0 to 40, with higher scores indicative of higher self-perceived resilience. The normative adult mean score in the United States is 31.8 (SD, 5.4), [62, 63] with an estimated minimal clinically important difference of 2.7. [64] Its Cronbach’s alpha was 0.90.

Symptom Measures

The 20-item CES-D evaluates the major symptoms in the clinical syndrome of depression. A total score can range from 0 to 60, with scores of $\geq$16 indicating the need for individuals to seek clinical evaluation for major depression. The CES-D has well established validity and reliability. [65-67] In this study, its Cronbach's alpha was 0.89.

The 20-items on the STAI-S and STAI-T were rated from 1 to 4. [68] The STAI-S measures a person's temporary anxiety response to a specific situation or how anxious or tense a person is "right now" in a specific situation. The STAI-T measures a person's predisposition to anxiety as part of one’s personality. Cut-off scores of $\geq$31.8 and $\geq$32.2 indicate a high level of trait and state anxiety, respectively. Cronbach's alphas for the STAI-T and STAI-S were 0.92 and 0.96, respectively.

The 18-item LFS was designed to assess physical fatigue and energy. [69] Each item was rated on a 0 to 10 NRS. Total fatigue and energy scores were calculated as the mean of the

13 fatigue items and the 5 energy items, respectively. Higher scores indicate greater fatigue severity and higher levels of energy. Using separate LFS questionnaires, patients were asked to rate each item based on how they felt within 30 minutes of awakening (i.e., morning fatigue, morning energy) and prior to going to bed (i.e., evening fatigue, evening energy). The LFS has established cut-off scores for clinically meaningful levels of fatigue (i.e., ≥3.2 for morning fatigue, ≥5.6 for evening fatigue) and energy (i.e., ≤6.2 for morning energy, ≤3.5 for evening energy). [70] Cronbach's alphas were 0.96 for morning and 0.93 for evening fatigue and 0.95 for morning and 0.93 for evening energy.

The 21-item GSDS was designed to assess the quality of sleep in the past week. [71] Each item was rated on a 0 (never) to 7 (everyday) NRS. The GSDS total score is the sum of the 21 items that can range from 0 (no disturbance) to 147 (extreme sleep disturbance). Higher total scores indicate higher levels of sleep disturbance. A GSDS total score of ≥43 indicates a significant level of sleep disturbance. [70] Cronbach's alpha for GSDS score was 0.83.

The 16-item AFI assesses an individual’s perceived effectiveness in performing daily activities that are supported by attention and working memory. [72] A higher total mean score on a 0 to 10 NRS indicates better cognitive function. [72] Total scores are grouped into categories of attentional function (i.e., <5 low function, 5.0 to 7.5 moderate function, >7.5 high function). [73] Cronbach’s alpha for the total AFI score was 0.93.

The occurrence of pain was evaluated using the Brief Pain Inventory. [74] Patients who responded yes to the question about having pain were asked to indicate if their pain was or was not related to their cancer treatment. Patients were categorized into one of four groups (i.e., no pain, only noncancer pain, only cancer pain, both cancer and noncancer pain). Patients rated the intensity of their worst pain using 0 (none) to 10 (excruciating) NRS. In addition, they provided information on pain’s level of interference with function.

Data analysis

Descriptive statistics and frequency distributions were generated for sample characteristics at enrollment using the SPSS version 28 (IBM Corporation, Armonk, New York). As was done previously, [75] unconditional LCA was used to identify shortness of breath profiles that characterized unobserved subgroups of patients (i.e., latent classes) over the six assessments. Before performing the LCA, patients who reported the occurrence of shortness of breath for ≤1 of the six assessments were identified and labeled as the "None" class (n=943, 70.5%). Then, the LCA was performed on the remaining 395 patients using MPlus™ Version 8.4. [76]

Estimation was carried out with full information maximum likelihood with standard error and a Chi square test that are robust to non-normality and non-independence of observations ("estimator=MLR"). Model fit was evaluated to identify the solution that best characterized the observed latent class structure with the BIC, VLRM, entropy, and latent class percentages that were large enough to be reliable. [77] Missing data were accommodated for with the use of the EM algorithm. [78]

Differences among the latent classes in demographic, clinical, and symptom characteristics, as well as stress and resilience measures, were evaluated using parametric and nonparametric tests. A p-value of <.05 was considered statistically significant. Bonferroni corrected p-value of <.008 was considered statistically significant for the pairwise contrasts.

RESULTS

Latent class solution

As noted in our previous publication, [26] the 943 patients (70.5%) who had ≤1 occurrence of shortness of breath over the six assessments were classified as the None class. For the remaining 395 patients whose data were entered into the LCA, a three-class solution was selected because the BIC for that solution was lower than the BIC for the 2-class solution. In addition, the VLMR was significant for the 3-class solution, indicating that three classes fit the

data better than two classes. Shortness of breath classes were labeled based on their distinct trajectories for the occurrence: Decreasing (8.2%), Increasing (7.8%), and High (13.5%) (Supplemental Figure 1).

Demographic and clinical characteristics

As noted in our previous publication, [26] significant differences were found among the latent classes for many of the demographic and clinical characteristics (Supplemental Table 1). In brief, compared to the None class, the High class was more likely to live alone, less likely to be employed, and more likely to report a previous or current history of smoking. In addition, they were more likely to have multiple cancer treatments, more likely to have lung metastasis, more likely to be receiving chemotherapy on 21- or 28-day cycles, and more likely to self-report a diagnosis of osteoarthritis, back pain, and rheumatoid arthritis. Compared to the None class, the Decreasing and High classes had lower KPS scores, a higher number of comorbidities, higher SCQ scores, and were more likely to self-report a diagnosis of depression. Compared to the None and Decreasing classes, the High class was more likely to be older and more likely to have lung cancer.

Stress and resilience scores

Compared to the None class, the Decreasing and High classes reported higher PSS total, IES-R total, IES-R intrusion, IES-R hyperarousal, and LSC-R affected sum scores. Compared to the None class, the High class reported higher IES-R avoidance subscale and LSC-R total scores. Compared to the None and Increasing classes, the High class reported higher LSC-R PTSD sum scores and lower CDRS scores (Table 1).

Occurrence of SLEs

Compared to the None class, the High class reported higher occurrence rates for physical neglect, sexual harassment, being forced to touch and sex before the age of sixteen, and being separated or divorced. Compared to the None class, the Increasing and High classes reported higher occurrence rates for being forced to touch and sex at ≥ 16 years. Compared to

the None class, the Decreasing class reported a higher occurrence rate for having parents separated or divorced (Table 2).

Symptom severity scores

Compared to the None class, the other three classes reported higher levels of morning fatigue and sleep disturbance. Compared to the None class, the Decreasing and High classes reported higher levels of depressive symptoms, trait and state anxiety, cognitive dysfunction, and pain interference score, and decrements in morning energy. Compared to the None class, the Decreasing and High classes were more likely to have both cancer and non-cancer pain. Compared to the None class, the Increasing and High classes reported higher levels of evening fatigue. Compared to the None class, the High class reported a higher worst pain intensity score (Table 3).

DISCUSSION

As part of an extension of our previous study of subgroups of patients with distinct shortness of breath profiles, [26] this analysis is the first to describe associations between shortness of breath and three types of stress, as well as resilience in a sample of patients with heterogeneous types of cancer. Equally important, associations between shortness of breath and common symptoms were evaluated. The common and distinct risk factors for shortness of breath across the Decreasing, Increasing, and High classes compared to the None class are summarized in Table 4. Given the paucity of research on shortness of breath in oncology patients, our results are compared with findings from the general population and patients with cardiopulmonary disease.

Stress measures

Compared to the None class, patients in the Decreasing and High classes reported higher levels of global stress. Similarly, in previous studies of palliative care patients [32] and adolescent patients with asthma, [79] the severity of shortness of breath was positively correlated with global stress. One potential explanation for this relationship, that warrants

additional investigation, is that both disruptions in the HPA axis and increases in systemic inflammation occur in oncology patients receiving chemotherapy that contribute to the occurrence of dyspnea. [32, 80]

In terms of cancer-related stress, compared to the None class, both the Decreasing and High classes reported higher IES-R total, intrusion, and hyperarousal scores. Of note, in the Decreasing and High classes, 23.1% and 14.0% met the criteria for partial PTSD and 14.4% and 23.4% met the criteria for PTSD, respectively. In addition, fears of recurrence and declines in physical function in oncology patients may contribute to the severity of PTSD symptoms. [34] These findings suggest that both cancer-related stress and relatively high levels of PTSD result in decreases in the threshold of dyspnea perception. This hypothesis is supported by a study that found that individuals who had PTSD following the World Trades Center disaster were twice as likely to experience shortness of breath than individuals without PTSD. [81]

While the Decreasing and High classes showed similar trends in the severity of global and cancer-specific stress at enrollment, no explanation is readily apparent for why this pattern was not observed in the Increasing class. The distinct trajectories of shortness of breath for the Increasing and Decreasing classes may be explained by differences in the provision of timely symptom management inventions (e.g., steroids, oxygen, opioids, thoracentesis); different etiologies for shortness of breath (e.g., anemia, pleural effusion); and/or the presence of a variety of triggers (e.g., smoking, air pollution). If these trajectories are replicated in an independent sample, additional phenotypic characteristics and interventions warrant evaluation to determine the specific risk factors for membership in the Increasing class.

In terms of the overall number of SLEs, as well as the occurrence of specific SLEs, the primary differences were between the None and the High classes. Specifically, the High class reported higher occurrence rates for physical neglect, sexual harassment, forced to touch at less than 16 years, forced sex at less than 16 years of age, and being separated or divorced. In addition, compared to the None and Increasing classes, the High class reported a higher LSC-R

PTSD sum score. Our findings are consistent with previous reports that found that individuals who experienced interpersonal violence, abuse, and neglect had higher levels of PTSD symptoms, compared to those with other types of traumas (e.g., unexpected death of a loved one). [82]

These findings suggest that for the High class in particular, the cumulative impact of various types of stress, particularly adverse childhood experiences (ACEs) may contribute to the occurrence of shortness of breath in patients receiving chemotherapy. Accumulating evidence suggests that exposure to early psychological stress contributes to the lifelong responsiveness of the HPA axis to stress. [83] Specifically, repeated activation of the HPA axis may result in blunted cortisol responses to a variety of stressors (e.g., airway inflammation). [31] Over time, reduced inhibitory feedback associated with stress contributes to airway sensitization and chronic/refractory dyspnea. [31] This hypothesis is supported by a study of the general population [84] that found that exposure to a higher number of traumatic events and the occurrence of PTSD were associated with increased airflow limitations. [85] Given the paucity of research on associations between dyspnea and SLEs in oncology patients, additional mechanistic studies are warranted.

Co-occurring symptoms

Anxiety is hypothesized to play a crucial role in dyspnea perception. [86] Specifically, anxiety is known to amplify shortness of breath by increasing anxiety sensitivity (i.e., the fear of anxiety symptoms [87]) and activating the limbic system. [88, 89] Therefore, it is not surprising that across our four distinct shortness of breath profiles, both trait and state anxiety scores exceeded the clinically meaningful cutoffs. Our findings are supported by a study of healthy volunteers, [90] that found that higher trait anxiety was associated with dyspnea unpleasantness, as well as higher state anxiety levels. Additional investigations are warranted on the common and distinct roles of trait and state anxiety in the affective dimension of shortness of breath.

Depressive symptoms scores approached or exceeded cutoff scores only for the Decreasing and High classes. Evidence suggests that depression decreases the threshold of shortness of breath by altering the perception of respiratory sensations. [89] Of note, in studies of patients with COPD, [91, 92] depression scores were positively correlated with the frequency of shortness of breath; functional impairment related to shortness of breath; emotional and cognitive responses to shortness of breath; and catastrophic thinking. In addition, in a study of patients with lung cancer that used latent variable modeling to create subgroups of patients with distinct functional status profiles, [37] patients with the Severe Disability profile reported higher levels of shortness of breath and depressive symptoms. In terms of interventions for the co-occurrence of dyspnea and depression, in a study of patients with advanced cancer, [93] the administration of sertraline resulted in decreases over time in the severity of both depression and shortness of breath. Additional research is warranted on the efficacy of antidepressants to decrease one or both of these symptoms.

Consistent with previous findings, [15, 16, 39, 42, 44] morning fatigue scores exceeded clinically meaningful cutoffs in the Decreasing, Increasing, and High classes. This finding is not surprising, given that compared to the None class, these patients reported higher levels of sleep disturbance. In terms of evening fatigue, while all three classes of patients with shortness of breath had scores above the clinically meaningful cutoff, only the Decreasing and High classes had higher scores than the None class. Additional research is warranted to understand the specific causes of fatigue associated with shortness of breath in patients undergoing chemotherapy (e.g., respiratory muscle weakness, hypoxia).

Consistent with four studies, [11, 21, 24, 42] patients in the High class reported higher worst pain scores. In addition, patients in the Decreasing and High classes were more likely to have both cancer and noncancer pain. This finding is aligned with a longitudinal study of a large cohort of Medicare recipients that reported that compared to individuals without dyspnea, individuals with the symptom had higher pain prevalence rates (i.e., 18% versus 64%). [94] In

addition, individuals with chest, back, or arthritis pain were substantially more likely to report dyspnea. Of note, the relative risk of dyspnea resolving was greatly increased if the pain problem resolved. One potential explanation for this association is that long-term physical inactivity associated with chronic pain results in physical deconditioning and secondary shortness of breath. [94] Another potential explanation for the inter-connectedness between the two symptoms is that the perceptions of pain and shortness of breath activate similar brain cortical regions and shares common neural mechanisms. [95, 96]

While patients in all four of our shortness of breath profiles had GSDS scores above the clinically meaningful cutoff, consistent with two studies of patients with advanced cancer, [15, 39] compared to the None class, the other three classes reported higher levels of sleep disturbance. Of note, normal human sleep causes a rapid and shallow breathing pattern; an unpredictable depth of breathing; a significant decrease in tidal volume; and decrements in ventilation and gas exchange during rapid eye movement sleep. [97] Given the inter-connectedness between sleep and respiration, shortness of breath during the night may contribute to decrements in sleep duration and sleep quality and increases in daytime tiredness (i.e., morning fatigue). In terms of potential interventions, in a study of patients with COPD, [98] progressive relaxation exercises improved dyspnea, fatigue, and sleep disturbance. The improvements in all three symptoms may be the result of increases in lung function and skeletal muscle relaxation, and/or decreases in stress.

Consistent with a previous finding in patients with COPD, asthma, or heart failure, [48] higher occurrence rates of shortness of breath were associated with more severe decrements in cognitive function on our sample. In addition, in a study of healthy volunteers, [99] experimentally-induced dyspnea interfered with cognitive function. In other studies of community-dwelling older adults [100] and patients with COPD, [101] the co-occurrence of depression, anxiety, and sleep disturbance was associated with decrements in cognitive function.

Resilience

All four of our classes had CDRS scores below the normative data for adults in the United States. [63] Specifically, compared to the None and Increasing classes, the High class had significantly lower resilience scores. Given that the High class reported a higher comorbidity burden, a lower functional status, a lower level of social support, and poorer quality of life, [26] this finding is not surprising. Likewise, in patients with pulmonary disease, [102] lower levels of resilience were correlated with higher levels of anxiety and depression and lower quality of life scores. Repetitive episodes of shortness of breath may cause fear that leads to the avoidance of daily activity or social interactions, neuropsychological symptoms, and decreases in resilience. [15, 103, 104] However, because social buffering may modulate HPA reactivity to stressors, [105] resilience training may decrease shortness of breath in oncology patients. [106]

LIMITATIONS

Several limitations warrant consideration. Given that our sample was relatively homogenous in terms of gender, race, and ethnicity, our findings may not generalize to more diverse racial and ethnic groups. While this study used a valid and reliable measure to assess the subjective experience of shortness of breath, future studies need to evaluate for correlations with objective measures of pulmonary function and/or neuroimaging. In addition, detailed information is needed on the etiology of shortness of breath and the use of pharmacologic and nonpharmacologic treatments. Finally, a more detailed evaluation of demographic and clinical characteristics associated with membership in the Increasing class warrants investigation.

CONCLUSIONS

Despite these limitations, this study provides new information on the role of stress, resilience, and co-occurring symptoms in the occurrence of shortness of breath in a large sample of patients with heterogenous types of cancer. While some risk factors associated with shortness of breath in the Decreasing and High classes were similar, the High class reported higher rates of ACEs that may contribute to the higher rates of shortness of breath. Additional

mechanistic studies may increase our understanding of differences among the distinct shortness of breath profiles.

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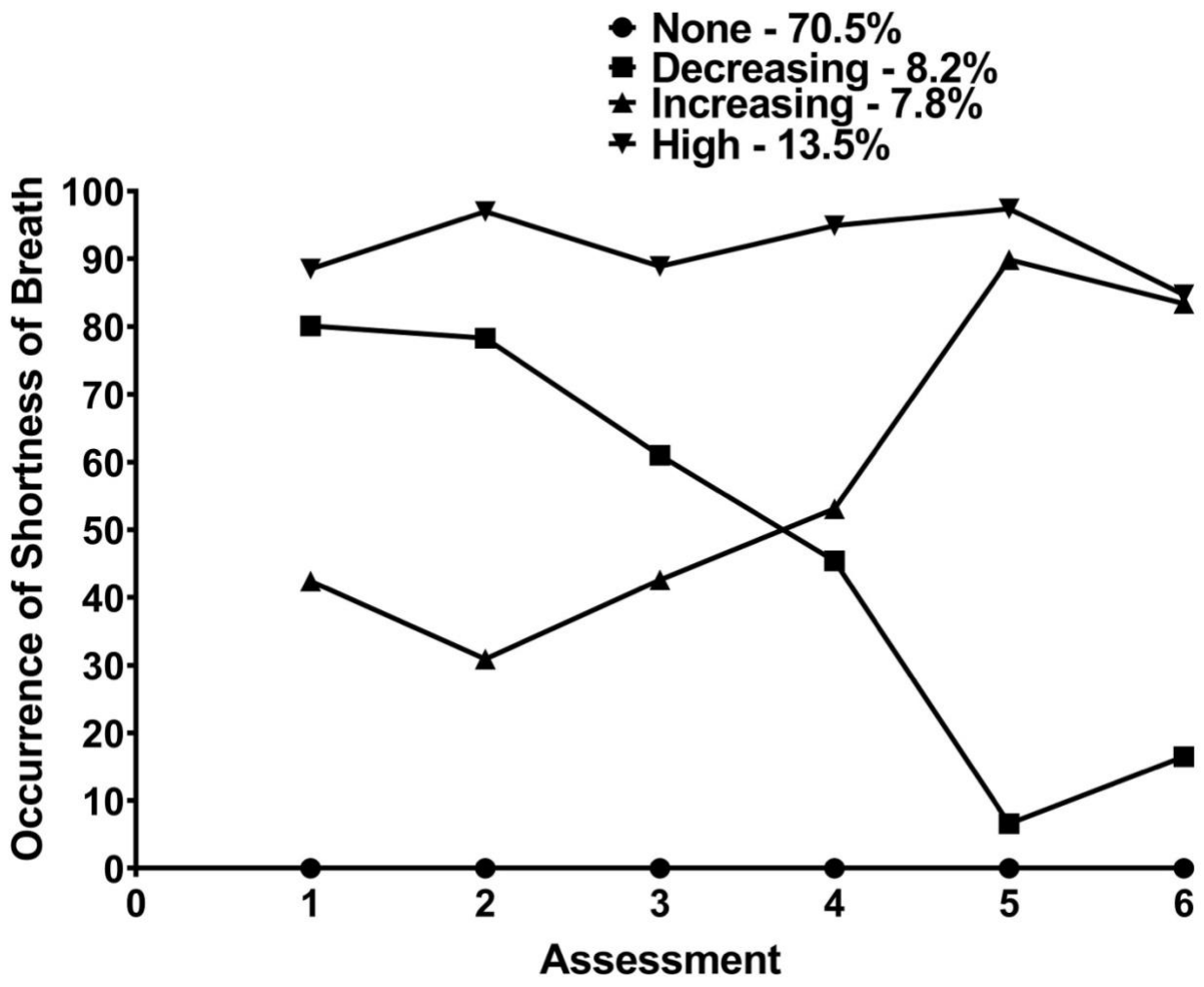

Supplemental Figure 5.1. Trajectories of shortness of breath occurrence for the four latent class

Table 5.1. Differences in Co-Occurring Symptom Severity Scores at Enrollment Among the Shortness of Breath Latent Classes

Symptoms[a]	**None (0) 70.5% (n=934)**	**Decreasing (1) 8.2% (n=109)**	**Increasing (2) 7.8% (n=105)**	**High (3) 13.5% (n=181)**	**Statistics**
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Depressive symptoms (≥16.0)	11.7 (9.1)	15.9 (11.0)	13.9 (10.3)	16.3 (10.4)	F = 16.47, p <.001 0 < 1 and 3
Trait anxiety (≥31.8)	34.1 (10.0)	38.0 (10.5)	35.1 (10.9)	38.8 (11.5)	F = 13.08, p <.001 0 < 1 and 3, 2 < 3
State anxiety (≥32.2)	32.9 (11.7)	36.5 (13.9)	33.6 (13.4)	37.6 (13.2)	F = 8.93, p <.001 0 < 1 and 3
Morning fatigue (≥3.2)	2.8 (2.2)	4.3 (2.1)	3.7 (2.3)	3.9 (2.3)	F = 26.70, p <.001 0 < 1, 2, and 3
Evening fatigue (≥5.6)	5.2 (2.2)	5.7 (2.0)	5.9 (1.9)	5.7 (1.9)	F = 6.82, p <.001 0 < 2 and 3
Morning energy (≤6.2)	4.6 (2.3)	4.0 (2.0)	4.1 (2.3)	3.9 (2.0)	F = 7.49, p <.001 0 > 1 and 3
Evening energy (≤3.5)	3.6 (2.0)	3.7 (2.0)	3.2 (2.2)	3.5 (2.0)	F = 1.04, p = .375
Sleep disturbance (≥43.0)	50.0 (20.0)	58.5 (19.9)	55.8 (18.7)	59.8 (19.9)	F = 16.91, p <.001 0 < 1, 2, and 3
Attentional function (<5.0 = Low, 5 to 7.5 = Moderate, >7.5 = High)	6.6 (1.8)	5.6 (1.7)	6.4 (1.8)	5.9 (1.8)	F = 15.03, p <.001 0 > 1 and 3, 1 < 2
	% (n)	% (n)	% (n)	% (n)	
Type of pain					X^2 = 42.55, p<.001
No pain	30.5 (282)	17.9 (19)	27.9 (29)	16.4 (29)	0 > 1 and 3
Only noncancer pain	25.6 (237)	27.4 (29)	22.1 (23)	32.2 (57)	NS
Only cancer pain	17.7 (164)	11.3 (12)	12.5 (13)	11.3 (20)	NS
Both cancer and noncancer pain	26.2 (243)	43.4 (46)	37.5 (39)	40.1 (71)	0 < 1 and 3
For patients with pain	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Worst pain score	5.9 (2.5)	6.5 (2.5)	6.1 (2.9)	6.7 (2.4)	F = 4.55, p = .004 0 < 3
Mean pain interference score	2.7 (2.4)	3.7 (2.8)	3.3 (2.6)	4.2 (2.4)	F = 15.77, p <.001 0 < 1 and 3

[a]Clinically meaningful cutoff scores

Abbreviations: SD = standard deviation

Table 5.2. Differences in Stress and Resilience Measures Among the Shortness of Breath Latent Classes at Enrollment

Measures[a]	**None (0) 70.5% (n=934)**	**Decreasing (1) 8.2% (n=109)**	**Increasing (2) 7.8% (n=105)**	**High (3) 13.5% (n=181)**	**Statistics**
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
PSS total score (range 0 to 56)	17.8 (8.0)	20.7 (8.2)	18.7 (8.3)	20.9 (8.1)	F = 10.19, p <.001 0 < 1 and 3
IES-R total score (≥24.0 – clinically meaningful PTSD symptomatology) (≥33.0 – probable PTSD)	17.5 (11.9)	21.7 (14.9)	19.9 (15.2)	23.2 (15.6)	F = 11.68, p <.001 0 < 1 and 3
IES-R intrusion	0.8 (0.6)	1.1 (0.8)	1.0 (0.8)	1.1 (0.8)	F = 10.46, p <.001 0 < 1 and 3
IES-R avoidance	0.9 (0.6)	1.0 (0.7)	1.0 (0.7)	1.1 (0.7)	F = 3.58, p =.013 0 < 3
IES-R hyperarousal	0.6 (0.6)	0.9 (0.8)	0.7 (0.8)	0.9 (0.8)	F = 15.14, p <.001 0 < 1 and 3
LSC-R total score (range 0–30)	5.7 (3.6)	6.7 (4.5)	6.5 (4.4)	7.4 (4.5)	F = 8.91, p <.001 0 < 3
LSC-R affected sum score (range 0-150)	10.8 (9.5)	14.1 (13.8)	13.0 (12.3)	15.2 (13.0)	F = 8.56, p <.001 0 < 1 and 3
LSC-R PTSD sum score (range 0-21)	2.8 (2.7)	3.6 (3.7)	3.1 (3.1)	4.2 (3.7)	F = 8.94, p <.001 0 and 2 < 3
CDRS total score (range 0–40) (31.8 (±5.4) – normative mean score for the United States population)	30.3 (6.4)	28.9 (6.3)	31.3 (5.7)	28.8 (6.4)	F = 5.23, p =.001 0 and 2 > 3, 1 < 2

Abbreviations: CDRS = Connor Davidson Resilience Scale, IES-R = Impact of Event Scale – Revised, LSC-R = Life Stressor Checklist-Revised, PSS = Perceived Stress Scale, PTSD = post-traumatic stress disorder, SD = standard deviation

[a]Clinically meaningful cutoff scores or range of scores

Table 5.3. Differences Among the Shortness of Breath Latent Classes in the Percentage of Patients Exposed to Specific Stressors

Stressful Life Event	**None (0) 70.5% (n=943)**	**Decreasing (1) 8.2% (n=109)**	**Increasing (2) 7.8% (n=105)**	**High (3) 13.5% (n=181)**	**Statistics**
	% (n)	% (n)	% (n)	% (n)	
Interpersonal Violence, Abuse, and Neglect Stressors					
Family violence in childhood	22.7 (161)	26.4 (23)	17.8 (16)	31.2 (43)	$X^2 = 6.73$, p = .081
Emotional abuse	19.4 (138)	25.6 (23)	24.2 (22)	29.1 (41)	$X^2 = 7.83$, p = .050
Physical neglect	3.7 (26)	8.8 (8)	3.3 (3)	9.3 (13)	$X^2 = 11.69$, p = .009 0 < 3
Sexual harassment	15.1 (106)	22.5 (20)	24.2 (22)	27.1 (38)	$X^2 = 15.41$, p = .001 0 < 3
Physical abuse - <16 years	12.3 (87)	21.3 (19)	16.5 (15)	18.4 (26)	$X^2 = 8.18$, p = .042 no significant pairwise contrasts
Physical abuse - ≥16 years	12.2 (86)	19.3 (17)	14.3 (13)	15.7 (22)	$X^2 = 4.22$, p = .239
Forced to touch - <16 years	9.2 (65)	13.5 (12)	15.7 (14)	19.9 (28)	$X^2 = 14.91$, p = .002 0 < 3
Forced to touch - ≥16 years	4.4 (31)	7.9 (7)	11.1 (10)	9.9 (14)	$X^2 = 11.61$, p = .009 0 < 2 and 3
Forced sex - <16 years	2.8 (20)	7.8 (7)	5.6 (5)	9.2 (13)	$X^2 = 14.53$, p = .002 0 < 3
Forced sex - ≥16 years	4.8 (34)	6.7 (6)	12.2 (11)	10.6 (15)	$X^2 = 12.16$, p = .007 0 < 2 and 3
Other Stressors					
Been in a serious disaster	40.3 (286)	41.1 (37)	42.9 (39)	42.4 (59)	$X^2 = 0.40$, p = .941
Seen serious accident	31.9 (227)	26.7 (24)	31.9 (29)	41.1 (58)	$X^2 = 6.27$, p = .099
Had serious accident or injury	23.2 (163)	23.3 (21)	25.6 (23)	29.3 (41)	$X^2 = 2.49$, p = .477
Jail (family member)	18.3 (130)	26.7 (24)	26.7 (24)	24.5 (34)	$X^2 = 7.65$, p = .054
Jail (self)	6.3 (45)	8.9 (8)	6.7 (6)	7.8 (11)	$X^2 = 1.12$, p = .773
Foster care or put up for adoption	2.2 (16)	2.2 (2)	3.3 (3)	2.8 (4)	$X^2 = 0.51$, p = .917
Separated/divorced (parents)	19.2 (137)	31.5 (28)	25.3 (23)	26.2 (37)	$X^2 = 10.02$, p = .018 0 < 1
Separated/divorced (self)	33.4 (239)	41.1 (37)	35.6 (32)	47.1 (66)	$X^2 = 10.69$, p = .014 0 < 3
Serious money problems	18.2 (130)	21.1 (19)	24.7 (22)	24.8 (35)	$X^2 = 4.80$, p = .187
Had serious physical or mental illness (not cancer)	16.9 (121)	20.9 (19)	22.0 (20)	26.1 (37)	$X^2 = 7.34$, p = .062
Abortion or miscarriage	43.8 (236)	46.9 (38)	41.3 (31)	46.2 (55)	$X^2 = 0.73$, p = .867
Separated from child	1.6 (11)	2.3 (2)	3.4 (3)	3.7 (5)	$X^2 = 3.21$, p = .360
Care for child with handicap	3.8 (26)	4.6 (4)	3.4 (3)	4.4 (6)	$X^2 = 0.31$, p = .958

Table 5.3. Differences Among the Shortness of Breath Latent Classes in the Percentage of Patients Exposed to Specific Stressors

Stressful Life Event	**None (0) 70.5% (n=943)**	**Decreasing (1) 8.2% (n=109)**	**Increasing (2) 7.8% (n=105)**	**High (3) 13.5% (n=181)**	**Statistics**
	% (n)	% (n)	% (n)	% (n)	
Care for someone with severe physical or mental handicap	22.9 (161)	23.9 (21)	23.9 (21)	32.6 (45)	$X^2 = 5.88$, p = .117
Death of someone close (sudden)	49.0 (344)	51.7 (46)	50.5 (46)	48.9 (67)	$X^2 = 0.29$, p = .962
Death of someone close (not sudden)	78.9 (551)	76.7 (66)	79.5 (70)	80.6 (112)	$X^2 = 0.49$, p = .921
Seen robbery/mugging	21.2 (151)	23.6 (21)	18.7 (17)	27.3 (38)	$X^2 = 3.28$, p = .350
Been robbed/mugged	25.6 (181)	30.3 (27)	30.8 (28)	26.6 (37)	$X^2 = 1.78$, p = .619

Table 5.4. Characteristics Associated with Membership in the Decreasing, Increasing, and High Shortness of Breath Classes

Characteristic[a]	Decreasing	Increasing	High
Symptom Characteristics			
Higher depressive symptoms	■		■
Higher trait anxiety	■		■
Higher state anxiety	■		■
Higher morning fatigue	■	■	■
Higher evening fatigue		■	■
Lower morning energy	■		■
Higher sleep disturbance	■	■	■
Lower attentional function	■		■
Less likely not to have pain	■		■
More likely to have both cancer and noncancer pain	■		■
Higher worst pain score			■
Higher mean pain interference score	■		■
Stress and Resilience Measures			
Higher Perceived Stress Scale score	■		■
Higher Impact of Event Scale-Revised total score	■		■
Higher Impact of Event Scale-Revised intrusion score	■		■
Higher Impact of Event Scale-Revised avoidance score			■
Higher Impact of Event Scale-Revised hyperarousal score	■		■
Higher Life Stressor Checklist-Revised total score			■
Higher Life Stressor Checklist-Revised affected sum score	■		■
Higher Life Stressor Checklist-Revised PTSD sum score			■
Lower Connor Davidson Resilience Scale total score			■
Higher Occurrence of Interpersonal Violence, Abuse, and Neglect Stressors			
Physical neglect			■
Sexual harassment			■
Forced to touch - <16 years			■
Forced to touch - ≥16 years		■	■
Forced sex - <16 years			■
Forced sex - ≥16 years		■	■
Higher Occurrence of Other Stressors			
Separated/divorced (parents)	■		
Separated/divorced (self)			■

[a]Comparisons done with the None group
■ – indicates that the class had this characteristic compared to the None class
Abbreviations: PTSD = post-traumatic stress disorder

Supplementary Table 5.1. Differences in Demographic and Clinical Characteristics at Enrollment Among the Shortness of Breath Latent Classes at Enrollment

Characteristic	None (0) 70.5% (n=943)	Decreasing (1) 8.2% (n=109)	Increasing (2) 7.8% (n=105)	High (3) 13.5% (n=181)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	57.0 (12.3)	55.3 (13.0)	56.5 (12.2)	59.6 (12.0)	F = 3.44, p = .016 0 and 1 < 3
Education (years)	16.3 (3.0)	15.8 (2.8)	16.1 (3.0)	16.2 (3.1)	F = 0.69, p = .558
Body mass index (kilogram/meter squared)	25.9 (5.4)	26.2 (6.4)	27.4 (6.5)	26.8 (6.0)	F = 3.05, p = .028 no significant pairwise contrasts
Alcohol Use Disorders Identification Test score	3.1 (2.5)	2.9 (2.3)	2.5 (2.5)	2.8 (2.5)	F = 1.11, p = .346
Karnofsky Performance Status score	81.7 (12.0)	75.4 (12.4)	78.9 (12.9)	74.7 (12.7)	F = 21.31, p <.001 0 > 1 and 3, 2 > 3
Number of comorbid conditions	2.2 (1.3)	2.7 (1.6)	2.5 (1.5)	3.1 (1.6)	F = 21.05, p <.001 0 < 1 and 3, 2 < 3
Self-administered Comorbidity Questionnaire score	5.1 (2.8)	6.2 (3.5)	5.8 (3.6)	7.1 (4.0)	F = 24.27, p <.001 0 < 1 and 3, 2 < 3
Time since diagnosis (years)	1.7 (3.2)	2.7 (5.5)	2.3 (4.0)	2.8 (5.3)	KW = 10.42, p = .015 no significant pairwise contrasts
Time since diagnosis (years, median)	0.41	0.50	0.44	0.51	
Number of prior cancer treatments	1.5 (1.4)	1.9 (1.7)	1.7 (1.5)	1.8 (1.7)	F = 4.27, p = .005 0 < 3
Number of metastatic sites including lymph node involvement[a]	1.2 (1.2)	1.2 (1.2)	1.3 (1.2)	1.4 (1.4)	F = 1.06, p = .365
Number of metastatic sites excluding lymph node involvement	0.8 (1.0)	0.8 (1.0)	0.8 (1.1)	1.0 (1.2)	F = 1.84, p = .138

Supplementary Table 5.1. Differences in Demographic and Clinical Characteristics at Enrollment Among the Shortness of Breath Latent Classes at Enrollment

Characteristic	None (0) 70.5% (n=943)	Decreasing (1) 8.2% (n=109)	Increasing (2) 7.8% (n=105)	High (3) 13.5% (n=181)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
MAX2 score	0.17 (0.08)	0.17 (0.08)	0.18 (0.08)	0.18 (0.09)	F = 0.60, p = .613
	% (n)	% (n)	% (n)	% (n)	
Gender (% female)	75.2 (708)	89.0 (97)	84.8 (89)	80.7 (146)	X^2 = 15.51, p = .001 0 < 1
Self-reported ethnicity White Asian or Pacific Islander Black Hispanic, Mixed, or Other	 69.6 (649) 13.2 (123) 6.6 (62) 10.6 (99)	 61.7 (66) 14.0 (15) 12.1 (13) 12.1 (13)	 67.0 (69) 13.6 (14) 7.8 (8) 11.7 (12)	 76.4 (136) 7.3 (13) 6.7 (12) 9.6 (17)	X^2 = 11.41, p = .249
Married or partnered (% yes)	67.0 (623)	62.6 (67)	52.9 (54)	58.9 (106)	X^2 = 11.10, p = .011 0 > 2
Lives alone (% yes)	19.7 (183)	17.6 (19)	30.1 (31)	28.5 (51)	X^2 = 12.50, p = .006 0 < 3
Currently employed (% yes)	37.3 (348)	30.6 (33)	34.6 (36)	26.7 (48)	X^2 = 8.66, p = .034 0 > 3
Annual household income Less than $30,000$^+$ $30,000 to $70,000 $70,000 to $100,000 Greater than $100,000	 14.8 (125) 21.2 (179) 17.4 (147) 46.6 (394)	 28.9 (28) 18.6 (18) 14.4 (14) 38.1 (37)	 26.4 (24) 24.2 (22) 13.2 (12) 36.3 (33)	 26.1 (43) 20.0 (33) 18.2 (30) 35.8 (59)	KW = 19.53, p <.001 0 > 2 and 3
Child care responsibilities (% yes)	22.8 (211)	22.9 (24)	22.8 (23)	18.2 (32)	X^2 = 1.86, p = .602
Elder care responsibilities (% yes)	7.4 (64)	7.4 (7)	14.1 (14)	7.0 (11)	X^2 = 5.78, p = .123
Past or current history of smoking (% yes)	32.9 (306)	37.0 (40)	37.6 (38)	45.5 (81)	X^2 = 10.76, p = .013 0 < 3

Supplementary Table 5.1. Differences in Demographic and Clinical Characteristics at Enrollment Among the Shortness of Breath Latent Classes at Enrollment

Characteristic	None (0) 70.5% (n=943)	Decreasing (1) 8.2% (n=109)	Increasing (2) 7.8% (n=105)	High (3) 13.5% (n=181)	Statistics
	% (n)	% (n)	% (n)	% (n)	
Level of exercise					$X^2 = 7.66$, p = .264
Does not exercise on a regular basis	35.1 (251)	40.9 (36)	39.2 (31)	43.5 (64)	
Exercises less than 150 minutes per week	45.1 (323)	35.2 (31)	44.3 (35)	41.5 (61)	
Exercises 150 or more minutes per week	19.8 (142)	23.9 (21)	16.5 (13)	15.0 (22)	
Specific comorbid conditions (% yes)					
Heart disease	5.1 (48)	6.4 (7)	3.8 (4)	9.9 (18)	$X^2 = 7.45$, p = .059
High blood pressure	30.1 (284)	32.1 (35)	25.7 (27)	32.6 (59)	$X^2 = 1.68$, p = .641
Lung disease	7.5 (71)	14.7 (16)	10.5 (11)	29.3 (53)	$X^2 = 73.16$, p <.001 0, 1, & 2 < 3
Diabetes	8.2 (77)	15.6 (17)	7.6 (8)	10.5 (19)	$X^2 = 7.30$, p= .063
Ulcer or stomach disease	4.5 (42)	5.5 (6)	4.8 (5)	6.6 (12)	$X^2 = 1.66$, p = .645
Kidney disease	1.1 (10)	1.8 (2)	1.0 (1)	3.3 (6)	$X^2 = 5.81$, p = .121
Liver disease	6.0 (57)	5.5 (6)	9.5 (10)	7.2 (13)	$X^2 = 2.23$, p = .526
Anemia or blood disease	10.3 (97)	19.3 (21)	18.1 (19)	14.9 (27)	$X^2 = 12.90$, p= .005 0 < 1
Depression	15.4 (145)	27.5 (30)	22.9 (24)	32.0 (58)	$X^2 = 33.90$, p <.001 0 < 1 and 3
Osteoarthritis	10.4 (98)	11.9 (13)	16.2 (17)	19.3 (35)	$X^2 = 13.07$, p = .004 0 < 3
Back pain	22.2 (209)	33.0 (36)	31.4 (33)	36.5 (66)	$X^2 = 22.02$, p <.001 0 < 3
Rheumatoid arthritis	2.9 (27)	1.8 (2)	1.0 (1)	7.2 (13)	$X^2 = 11.93$, p = .008 0 < 3

Supplementary Table 5.1. Differences in Demographic and Clinical Characteristics at Enrollment Among the Shortness of Breath Latent Classes at Enrollment

Characteristic	None (0) 70.5% (n=943)	Decreasing (1) 8.2% (n=109)	Increasing (2) 7.8% (n=105)	High (3) 13.5% (n=181)	Statistics
	% (n)	% (n)	% (n)	% (n)	
Cancer diagnosis					X^2 = 76.19, p <.001
Breast cancer	38.4 (362)	51.4 (56)	46.7 (49)	39.8 (72)	NS
Gastrointestinal cancer	35.4 (334)	21.1 (23)	21.0 (22)	16.6 (30)	0 > 1, 2, & 3
Gynecological cancer	17.7 (167)	15.6 (17)	18.1 (19)	16.6 (30)	NS
Lung cancer	8.5 (80)	11.9 (13)	14.3 (15)	27.1 (49)	0 and 1 < 3
Co-occurrence of lung cancer and lung disease	56.3 (45)	61.5 (8)	40.0 (6)	79.6 (39)	X^2 = 10.68, p = .014 0 and 2 < 3
Prior cancer treatment					X^2 = 26.42, p = .002
No prior treatment	25.6 (235)	19.8 (21)	18.8 (19)	28.2 (50)	NS
Only surgery, CTX, or RT	43.6 (400)	41.5 (44)	46.5 (47)	31.6 (56)	0 > 3
Surgery and CTX, or surgery and RT, or CTX and RT	20.2 (185)	20.8 (22)	17.8 (18)	18.6 (33)	NS
Surgery and CTX and RT	10.6 (97)	17.9 (19)	16.8 (17)	21.5 (38)	0 < 3
Receipt of targeted therapy (% yes)	27.2 (251)	33.3 (36)	31.7 (33)	40.9 (72)	X^2 = 14.18, p = .003 0 < 3
Cycle length					KW = 24.14, p <.001 0 < 3
14 day cycle+	45.5 (425)	40.7 (44)	41.0 (43)	25.8 (46)	
21 day cycle	48.0 (449)	52.8 (57)	49.5 (52)	63.5 (113)	
28 day cycle	6.5 (61)	6.5 (7)	9.5 (10)	10.7 (19)	
Metastatic sites					X^2 = 7.15, p = .622
No metastasis	32.2 (299)	34.0 (36)	30.8 (32)	33.3 (60)	
Only lymph node metastasis	23.2 (216)	17.9 (19)	26.0 (27)	16.1 (29)	
Only metastatic disease in other sites	21.1 (196)	20.8 (22)	19.2 (20)	22.8 (41)	
Metastatic disease in lymph nodes and other sites	23.5 (219)	27.4 (29)	24.0 (25)	27.8 (50)	
Lung metastasis (% yes)	14.1 (89)	21.1 (15)	15.1 (11)	30.0 (36)	X^2 = 19.28, p <.001 0 < 3

Supplementary Table 5.1. Differences in Demographic and Clinical Characteristics at Enrollment Among the Shortness of Breath Latent Classes at Enrollment

Characteristic	None (0) 70.5% (n=943)	Decreasing (1) 8.2% (n=109)	Increasing (2) 7.8% (n=105)	High (3) 13.5% (n=181)	Statistics
	% (n)	% (n)	% (n)	% (n)	
Emetogenicity of the CTX regimen Minimal/low Moderate High	 18.1 (169) 63.2 (591) 18.7 (175)	 24.8 (27) 50.5 (55) 24.8 (27)	 19.0 (20) 56.2 (59) 24.8 (26)	 24.2 (43) 59.0 (105) 16.9 (30)	KW = 3.41, p = .332
Antiemetic regimen None Steroid alone or serotonin receptor antagonist alone Serotonin receptor antagonist and steroid NK-1 receptor antagonist and two other antiemetics	 7.2 (66) 19.5 (178) 49.0 (448) 24.3 (222)	 7.6 (8) 22.9 (24) 41.0 (43) 28.6 (30)	 5.9 (6) 23.5 (24) 46.1 (47) 24.5 (25)	 6.9 (12) 22.3 (39) 45.7 (80) 25.1 (44)	X^2 = 4.02, p = .910

[a]Total number of metastatic sites evaluated was 9.
[+]Reference group

Abbreviations: CTX = chemotherapy, KW = Kruskal Wallis, NK-1 = neurokinin-1, NS = not significant, RT = radiation therapy, SD = standard devi

Chapter 6

Perturbations in Inflammatory Pathways Are Associated with Shortness of Breath Profiles in Oncology Patients Receiving Chemotherapy

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ABSTRACT

Background: Dyspnea is a common and distressing symptom in patients with cancer. While dyspnea worsens quality of life and decreases overall survival, the mechanisms that underlie this symptom are largely unknown.

Methods: Given the paucity of research on underlying mechanism(s) for dyspnea in patients with cancer and the potential contribution of inflammatory mechanisms, whole transcriptome gene expression and pathway impact analyses were done to evaluate for associations between this symptom and perturbations in inflammatory pathways. To evaluate the interconnections between and among these inflammatory pathways, an unweighted knowledge network was created using the specific pathway maps. Three centrality measures (i.e., betweenness, closeness, degree) were calculated to gain insights into the structural importance of each node.

Results: Among 73 significantly perturbed Kyoto Encyclopedia of Genes and Genomes signaling pathways, 29 were related to inflammatory mechanisms. Among these pathways, the MAPK signaling pathway node had the highest closeness, betweenness, and degree scores. In addition, five common respiratory disease-related pathways, that may share mechanisms with cancer-related dyspnea, were perturbed.

Conclusion: This study is the first to identify associations between shortness of breath and a number of inflammatory pathways and the interconnections among these pathways. Findings from this data-driven study provide preliminary support for the hypothesis that pulmonary and systemic inflammation contribute to the occurrence of dyspnea in patients receiving chemotherapy. While our findings warrant confirmation, we hypothesize that the mechanisms that underlie dyspnea in oncology patients may be similar to other respiratory diseases.

Keywords: breathlessness; cancer; chemotherapy; dyspnea; gene expression; inflammation; knowledge network; pathway impact analysis; shortness of breath

INTRODUCTION

Dyspnea is a common and distressing symptom that occurs in 10% to 70% of patients with cancer. [1] While dyspnea worsens quality of life and decreases overall survival, [2-6] the mechanisms that underlie this symptom are largely unknown. [7] Given the state of the science, the National Comprehensive Cancer Network Palliative Care Guideline on Dyspnea [8] and the American Society of Clinical Oncology Guideline on the Management of Dyspnea in Advanced Cancer [9] recommended that research be done to determine the mechanisms that underlie dyspnea in order to be able to develop novel and targeted therapeutic interventions.

In terms of a plausible mechanistic hypothesis, airway inflammation and associated perturbations in vagal afferent neurons appear to play central roles in the development of dyspnea. [10] First, inflammation results in the activation of bronchopulmonary C-fibers that may induce dyspnea. [10] Second, inflammatory process induces airway wall remodeling that is characterized by smooth muscle proliferation. [10] This remodeling increases tension in airway smooth muscles and may contribute to the development of dyspnea. [10] In addition, airway inflammation leads to sensory neuroplasticity that can manifest in two ways. [10] First, changes in gene expression in the cell body of primary afferent neurons within the airways result in hyperexcitability. Second, long-lasting amplification of synaptic transmission can occur in response to a variety of inflammatory mediators.

In patients with cancer, tumor cells and cytotoxic drugs may contribute to the development of dyspnea through the stimulation of innate and adaptive immune mechanisms. [11, 12] This systemic response results in the activation of a number of inflammatory signaling pathways; the recruitment of acute and/or chronic inflammatory cells; and the destruction of bronchoalveolar structures. [13-15] Studies of patients with lung, [16] breast, [17] and gynecological [18] cancer found significant decreases in pulmonary function tests following the administration of chemotherapy. While these studies did not measure associations with

dyspnea, these reductions in pulmonary function tests are an indicator of pulmonary toxicity (i.e., lung damage) following cancer treatment. [19-22]

In addition, systemic inflammation may contribute to the development of dyspnea through its effects on skeletal muscles (e.g., diaphragm). [23] As note in one review, [24] inflammation can have direct effects on skeletal muscles through the activation of receptor-mediated intramuscular signaling pathways (e.g., JAK/STAT and p38 MAPK pathways). In addition, with chronic inflammation, changes occur in the microenvironment of skeletal muscle cells that result in skeletal muscle atrophy. [24] In a study of patients with advanced cancer, [25] increases in the severity of dyspnea were associated with lower levels of maximal inspiratory pressure, a measure of diaphragmatic strength. In two preclinical studies, [26, 27] systemic administration of a clinical dose of doxorubicin resulted in inflammation and weakness of the diaphragm. Based on these findings, it is reasonable to hypothesize that peripheral lung and systemic inflammation play a role in the development of dyspnea in patients with cancer receiving chemotherapy.

In terms of an evaluation of the molecular mechanisms of dyspnea in oncology patients, three candidate gene studies were identified. [28-30] In a study of patients with non-small cell lung cancer, [30] three SNPs in the BRCA1 gene were associated with the severity of dyspnea. In another study of lung cancer survivors, [29] the severity of dyspnea was associated with SNPs in IL-6 and IL-1β. In a study of patients with advanced cancer, [28] individuals who were homozygous for the rare allele in the 5-hydroxytryptamine receptor 3B gene were more likely to report severe dyspnea. While these studies provide some information on the molecular mechanisms of dyspnea, [28-30] no studies have evaluated for associations between the occurrence of dyspnea and gene expression perturbations in inflammatory pathways.

The wide range in prevalence rates suggests that a large amount of inter-individual variability exists in the occurrence of dyspnea. One approach that can be used to evaluate for distinct dyspnea profiles is latent variable modeling. In our recent study, LCA was done to

identify subgroups of patients with distinct dyspnea profiles. [31] Using occurrence data from 1338 patients undergoing chemotherapy, 70.5% did not report shortness of breath. Of the remaining 395 patients, three distinct shortness of breath profiles were identified (i.e., Decreasing (8.2%), Increasing (7.8%), High (13.5%)). In the current analysis, an extreme phenotype approach was used to evaluate for perturbed inflammatory pathways between the None and High classes. Then, a knowledge network was used to identify the most influential pathway, as well as patterns of interactions, between and among these inflammatory pathways. [32]

METHODS

Patients and Settings

This study is part of a larger, longitudinal study of the symptom experience of oncology outpatients. Eligible patients were ≥18 years of age; had a diagnosis of breast, gastrointestinal, gynecological, or lung cancer; had received chemotherapy within the preceding four weeks; were scheduled to receive at least two additional cycles of chemotherapy; were able to read, write, and understand English; and provided written informed consent. Patients were recruited from two Comprehensive Cancer Centers, one Veteran's Affairs hospital, and four community-based oncology programs.

Study Procedures

The study was approved by the Institutional Review Board at the University of California, San Francisco and at each of the study sites. Eligible patients were approached in the infusion unit during their first or second cycle of chemotherapy by a member of the research team to discuss study participation and obtain written informed consent. Of the 2234 patients approached, 1343 consented to participate (60.1% response rate). The major reason for refusal was being overwhelmed with their cancer treatment.

Of these 1343 patients, 1338 reported the occurrence of shortness of breath a total of six times over two chemotherapy cycles (i.e., prior to chemotherapy administration,

approximately 1 week after chemotherapy administration, and approximately 2 weeks after chemotherapy administration). All of the other measures and blood for RNA were collected at the enrollment assessment (i.e., prior to the second or third cycle of chemotherapy). For this analysis, a total of 717 patients provided a blood sample (Supplemental Figure 1). Of these 717 patients, 357 had their samples processed using RNA sequencing (i.e., RNA-seq sample) and 360 had their samples processed using microarray (i.e., microarray sample) technologies.

Instruments

Demographic and clinical characteristics

Patients completed a demographic questionnaire, KPS scale, [33] SCQ, [34] and AUDIT. [35] Toxicity of the chemotherapy regimen was rated using the MAX2 index. [36] Medical records were reviewed for disease and treatment information.

Shortness of breath measure

Shortness of breath item from the MSAS was used to assess for the occurrence of the symptom at each of the six assessments. [37]

Data Analysis

Latent class analysis

As reported previously, [31] LCA was used to identify unobserved subgroups of patients (i.e., latent classes) with distinct shortness of breath profiles over the six assessments. Before performing the LCA, patients who reported the occurrence of shortness of breath for ≤1 of the six assessments were identified and labeled the “None” class (n=943, 70.5%). Then, the LCA was performed on the remaining 395 patients using MPlus™ Version 8.4. [38] A three-class solution was selected because this solution fit the data better than the 2-class solution. For the current analysis, using an extreme phenotype approach, an evaluation of differentially perturbed pathways between patients in the None and High shortness of breath classes was performed.

Imputation process

Missing data for demographic and clinical characteristics were imputed by the k-nearest-neighbors method, with k=9. For continuous variables, the Euclidean distance was used to find the nearest neighbors. The imputed value was the weighted average of the nearest neighbors, with each weight originally exp(-dist(x,j)), after which the weights were scaled to one. For categorical variables, distance was 0 if the predictor and the neighbor had the same value and 1 if they did not. The imputed value was the mode of the nearest neighbors.

Demographic and clinical data

Demographic and clinical data from the two patient samples (i.e., RNA-seq, microarray) were analyzed separately. Differences in demographic and clinical characteristics between the patients in the None and High shortness of breath classes were evaluated using parametric and non-parametric tests. Significance corresponded to a p-value of <.05.

In order to not overfit the regression models, a select number of significant demographic and clinical characteristics were included using the smaller sample sizes for the two analyses. [39, 40] These variables were selected based on previous evidence of an association with dyspnea. [41] For the RNA-seq sample, four variables were included (i.e., KPS score, SCQ score, hemoglobin level, cancer diagnosis). For the microarray sample, three variables were included (i.e., KPS score, SCQ score, cancer diagnosis). Demographic and clinical characteristics included in the final model were selected using a backwards stepwise logistic regression approach based on the likelihood ratio test. The area under the curve of the receiver operating characteristic curves was used to gauge the overall adequacy of the logistic regression model for each sample. [42] All of these analyses were performed using R (version 4.2.1). [43]

Differential expression and PIA and knowledge network construction

The gene expression and PIA were performed based on our previous experience. [44, 45] In brief, differential expression was quantified using empirical Bayes models that were implemented separately using edgeR [46] for the RNA-seq sample and limma [47] for the

microarray sample. These analyses were adjusted for demographic and clinical characteristics that remained significant in the final logistic regression model. In addition, the models included surrogate variables to adjust for variations due to unmeasured sources. [48, 49] Expression loci were annotated with Entrez gene identifiers. Gene symbols were derived from the HUGO Gene Nomenclature Committee resource database. [50] The differential expression results were summarized as the log fold-change and p-value for each gene. Only genes that had a common direction of expression across the two samples were retained for subsequent analyses. Common genes were matched using gene symbol.

The PIA included potentially important biological factors (e.g., gene-gene interactions, flow signals in a pathway, pathway topologies), as well as the magnitude (i.e., log fold-change) and p-values from the differential expression analysis for each sample. [51] The PIA included the results of the differential expression analyses for all of the genes (i.e., cutoff free) that had a common direction of differential expression to determine pPERT using Pathway Express. [52] A total of 222 signaling pathways were defined using the KEGG database. [53] For each sample, a separate test was performed for each pathway. Next, Fisher's Combined Probability method was used to combine these results to obtain a single test (global) of the null hypothesis. [54, 55] The significance of the combined transcriptome-wide PIA was assessed using FDR of 0.025. [56] Then, the KEGG Orthology was used to classify the perturbed pathways related to inflammatory mechanisms (i.e., signal transduction, immune system, signal molecules and interaction, transport and catabolism, cell growth and death, and cell motility). [57]

Next, an unweighted knowledge network was created based on interconnections among the inflammatory pathways using KEGG pathway maps. A knowledge network is a multi-edge graph that combines heterogeneous information from several sources; provides information about the nature and degree of interactions between and/or among nodes; and allows for the identification of nodes that have structural importance. [32] Nodes were defined as perturbed

inflammatory signaling pathways identified in this analysis. Edges were defined as shared member(s) identified in KEGG pathway maps.

To gain insights into the structural importance of each node, scores for three centrality measures (i.e., betweenness, closeness, degree) were calculated using Cytoscape (version 3.9.1). [58] Betweenness refers to the number of shortest paths going through a node. Closeness refers to the distance between nodes. Degree refers to the number of edges connected to a node. [59, 60]

RESULTS

RNA-seq Performance

Of the 293 patients in the RNA-seq sample, 233 were in the None and 60 were in the High shortness of breath classes. Median library threshold size was 9,209,606 reads. Following the application of quality control filters, 15,967 genes were included in the final analysis. The common dispersion was estimated as 0.1943, yielding a biological coefficient of variation of 0.4407 well within the expected value for clinical samples. [61, 62]

Microarray Performance

Of the 295 patients in the microarray sample, 242 were in the None and 53 were in the High shortness of breath classes. All of these samples demonstrated good hybridization performance for biotin, background negative, and positive control assays on the arrays. Following quality control filters, 44,225 loci were included in the final analysis.

Demographic and Clinical Characteristics

Of the 293 patients in RNA seq sample (Table 1), compared to None class, High class was more likely to have a lower performance status, a higher number of comorbidities, a higher comorbidity burden, a lower AUDIT score, and lower hemoglobin and hematocrit levels. In addition, High class was more likely to self-report diagnoses of heart disease, lung disease, anemia or blood disease, or depression, and less likely to self-report a diagnosis of rheumatoid arthritis; was more likely to have lung cancer and less likely to have gastrointestinal cancer; and

was less likely to be prescribed an antiemetic regimen that contained a serotonin receptor antagonist and a steroid.

Of 295 patients in microarray sample (Table 2), compared to None class, High class had a lower performance status, a higher number of comorbidities, a higher comorbidity burden and a higher number of prior cancer treatments. In addition, High class had a lower annual household income; was more likely to self-report diagnoses of lung disease, depression, osteoarthritis, or back pain; was less likely to have gastrointestinal cancer; was more likely to have lung cancer; was more likely to have lung metastasis; and was more likely to receive chemotherapy on a 21-day cycle.

Logistic Regression Analyses

In the logistic regression analysis for the RNA-seq sample (Table 3), three variables were retained in the final model (i.e., KPS score, hemoglobin levels, cancer diagnosis) and were used as covariates in the gene expression analysis. Patients who had a lower functional status and lung cancer were more likely to belong to the High class.

In the logistic regression analysis for the microarray sample (Table 3), three variables were retained in the final model (i.e., KPS score, SCQ score, cancer diagnosis) and were used as covariates in the gene expression analysis. Patients who had a higher comorbidity burden were more likely to belong to the High class. Patients who had gastrointestinal cancer were less likely to belong to the High class.

Perturbed Inflammatory Signaling Pathways

The final differential expression models for the RNA seq and microarray samples each included two surrogate variables and three phenotypic characteristics. A total of 5130 genes and 4922 genes were included in the PIA analyses for the RNA seq and microarray samples, respectively. Using Fisher's Combined Probability method, across the two samples, 73 KEGG signaling pathways were significantly perturbed at an FDR of 0.025. As shown in Table 4, 29 of these pathways were related to inflammatory mechanisms (i.e., 13 for immune system; 2 for

signaling molecules and interaction; 7 for signal transduction; 3 for transport and catabolism; 3 for cell growth and death; and 1 for cell motility).

Knowledge Network

As shown in Figure 1, the shortness of breath knowledge network consisted of 26 nodes (i.e., pathways) and 60 edges (average number of neighbors = 4.62). Three pathways (i.e., viral protein interaction with cytokine and cytokine receptor, peroxisome, hippo signaling) were not included in the final knowledge network due to the lack of the interconnection with the other 26 pathways.

Signal transduction pathways grouped together within the knowledge network (blue circles). Subgroups of the other inflammatory pathways were connected through these signal transduction pathways (i.e., red circles = immune system; grey circles = signal molecules and interaction, transport and catabolism, cell growth and death, and cell motility). Given that higher scores for closeness suggest that these nodes have closer relationships with and more direct influence on other nodes within the network, [59, 60] Table 5 was organized in descending order for the closeness scores.

The MAPK signaling pathway node had the highest closeness, betweenness, and degree scores. The next ten pathways with the highest centrality scores were: JAK/STAT signaling, apoptosis, PI3K-Akt signaling, NK-cell mediated cytotoxicity, NET formation, NF-kappa B signaling, cytokine-cytokine receptor interaction, NOD-like receptor signaling, FoxO signaling, and chemokine signaling.

Perturbed Respiratory Disease-related Pathways

As noted in the Introduction, our initial hypothesis was that shortness of breath would be associated with perturbations in inflammatory pathways. An evaluation of the PIA results identified five respiratory disease-related pathways that were significantly perturbed (i.e., coronavirus disease, influenza A, tuberculosis, pertussis, and asthma, Table 6). In an exploratory analysis, the KEGG pathway maps for each of these perturbed respiratory disease-

related pathways were evaluated for the inclusion of inflammatory pathways. Table 7 summarizes the 14 common inflammatory pathways across these respiratory disease-related pathways and from our list of 29 inflammatory pathways for shortness of breath.

DISCUSSION

This study is the first to identify perturbations in inflammatory pathways associated with shortness of breath in oncology patients receiving chemotherapy. Of note, our a priori hypothesis regarding the role of inflammatory mechanisms for this symptom was supported. In addition, the knowledge network demonstrates that the majority of these inflammatory pathways interact with each other (Figure 1). This discussion focuses on the eleven inflammatory pathways with the highest closeness scores (i.e., higher influence). The classifications proposed in the KEGG Orthology for inflammatory mechanisms were used to categorize the eleven perturbed pathways and organize subsequent sections of the Discussion. [57]

Signal Transduction

Signal transduction is a biological process that cells use to respond to external stimuli (e.g., cytotoxic drugs, ROS). [63] It plays an important role in the coordination of a variety of cellular functions (e.g., proliferation, differentiation, migration). [63] During this process, external stimuli are transduced into cells through an ordered sequence of biochemical reactions that results in a signal cascade. [63] In this analysis, the signal transduction pathways with highest closeness scores were: MAPK signaling, JAK-STAT signaling, PI3K-Akt signaling, NF-kappa B signaling, and FoxO signaling.

MAPK signaling pathway

The MAPK signaling pathway node had the highest closeness, degree, and betweenness scores. These findings suggest that the MAPK signaling pathway may act as the most influential and essential signaling within the shortness of breath knowledge network. [64]

Each centrality measure provides a different type of evidence on the role a node may play in the network. Having the highest closeness score suggests that the MAPK pathway has

the closest relationship with the highest number of other pathways, [59] as well as a high level of “direct and indirect influence” [64] within the network. The highest betweenness score suggests that this node represents a “bottleneck” pathway. [65] As a ”bottleneck” pathway, MAPK signaling may play the role of a “bridge” [66] that can monitor communications between other nodes in the network. [67] Equally important, the highest degree score suggests that the MAPK pathway is a “hub” pathway. As a “hub” pathway, this node has more local effects on the immediate neighborhood nodes. [67] Taken together, these findings suggest that the MAPK pathway has the most significant “local influence” [67] within the shortness of breath knowledge network.

Consistent with our findings, evidence suggests that MAPK signaling plays a role in lung inflammation and in the development of lung injury. [68-70] Activation of this pathway by cytotoxic drugs, tumor mass, and/or other types of cellular stress leads to proliferation of phagocytes and their influx into the lungs and associated production of chemokines, cytokines, and oxidative stress. [71] These processes contribute to apoptosis of alveolar epithelial cells, alveolar epithelial cell injury, decreases in cell migration in airway smooth muscle, and loss of the pulmonary endothelial barrier. [71, 72] During these remodeling processes, a variety of inflammatory mediators activate vagal afferent neurons in the airways that may result in the sensation of shortness of breath. [73]

JAK-STAT signaling pathway

The JAK-STAT signaling pathway mediates intracellular messages to induce hematopoiesis and inflammation and controls on immune responses. [74] Based on its closeness score, the JAK-STAT signaling pathway was the second most influential node within the shortness of breath knowledge network. A plausible hypothesis for this finding is that a variety of cytokines produced as part of this pathway can induce pulmonary and systemic inflammation that contributes to shortness of breath. [74] This hypothesis is supported by a growing body of evidence that identified associations between dysregulations of JAK-STAT

signaling and pulmonary fibrosis. [75] In addition, in a study of genomic profiles of lung tumor samples, [76] perturbations in the JAK-STAT pathway were identified as a common mechanism for IPF-induced lung cancer. Equally important, JAK-STAT signaling modulates the polarization of T helper (Th) cells. [77] These Th cells are considered vital in adaptive immunity because they are required to activate lymphocytes. [78] In addition, they produce various types and higher amounts of cytokines that participate in lung inflammation. [79] In a murine model of silica-induced lung inflammation and fibrosis, [80] inhibition of JAK-STAT signaling was associated with an increase in lung function. Lung inflammation and pulmonary fibrosis were decreased through attenuation of the differentiation of CD4+ T cells into the Th 17 cells.

PI3K-Akt signaling pathway

A variety of cellular stressors (e.g., radiation) or toxic molecules (e.g., chemotherapy, smoking) can activate the PI3K-Akt signaling pathway. [81, 82] This pathway stimulates innate immune responses and mediates the infiltration of immune cells into injured tissues. [81] Evidence suggests that PI3K-Akt signaling is involved in the pathogenesis of pulmonary fibrosis, a condition associated with dyspnea. [82, 83] Specifically, the PI3K-Akt signaling pathway is involved in EMT, epithelial cell senescence, and apoptosis of epithelial cells. [82]

NF-kappa B signaling pathway

The NF-kappa B signaling pathway is activated by pro-inflammatory cytokines, pattern recognition receptors, and oxidative stress. [84] In terms of lung damage, NF-kappa B signaling induces pulmonary inflammation, coagulation, and airway cellular apoptosis. [85, 86] Dysregulated NF-kappa B signaling is associated with the progression of a variety of pulmonary diseases (e.g., pulmonary fibrosis, [87] lung cancer, [87] acute lung injury [88], chronic pulmonary obstructive disease [89]). In terms of the interactions between the NF-kappa B signaling and PI3K/Akt signaling, in a murine model of cardiopulmonary bypass-induced lung injury, [90] these two signaling pathways co-modulated apoptosis in the lungs. The pathologic

processes associated with both pathways may result in shortness of breath in patients with cancer.

FoxO signaling pathway

The FoxO signaling pathway is involved in the regulation of apoptosis, oxidative stress, and cytokine release in a wide variety of immune cells. [91] While stimulated by the MAPK pathway, the PI3K-Akt pathway inhibits FoxO signaling. [91] In a study that compared lung fibroblasts from patients with IPF to those from healthy donors, [92] a decrease in FoxO3 activity was found in the fibroblasts of patients with IPF. In addition, FoxO3 knockout mice with lung fibrosis, who received a bleomycin challenge, had an increase in pulmonary fibrosis and decreased lung function. While no study has reported on a direct relationship between shortness of breath and the FoxO pathway, given that dysregulation of this pathway is involved in the progression of pulmonary fibrosis suggests a positive association. In addition, and consistent with previous research, [93] the FoxO pathway was connected with the cellular senescence pathway in our network. Because cellular senescence results in the inhibition of tissue repair and accelerates tissue aging, it is thought to be a pathogenic mechanism for pulmonary fibrosis. [94, 95] The identification of perturbations in the FoxO pathway in the current analysis provides preliminary evidence of shared mechanism between dyspnea in patients with pulmonary fibrosis and cancer.

Immune System

Immune cells participate in innate and adaptive immune responses. [96] The binding of molecules (e.g., cytokines) to their receptors produces intracellular signals that change functional behaviors in immune cells. [97] The perturbed immune system pathways with the highest closeness scores included: NK cell-mediated cytotoxicity, NET formation, NOD-like receptor signaling, and chemokine signaling.

NK cell-mediated cytotoxicity pathway

NK cells are innate lymphocytes that can kill target cells. [98, 99] The development and maturation of NK cells and their cytotoxic functions depend on a number of cytokines. [100] The production of cytokines in NK cells is mediated by MAPK signaling. [101] A growing body of evidence suggests that NK cells play important roles in lung inflammation. [99] The recruitment of NK cells to inflamed lung tissues produces multiple cytokines and chemokines and causes damage to lung tissues. [98, 99] These changes in lung structure result in impaired gas exchange and the development of shortness of breath.

NET formation pathway

NETs are formed through lytic NETosis, that involves the loss of cell membrane activity. [102] Microorganisms and/or endogenous stimuli (e.g., immune complexes, DAMPs) trigger NET formation. [102] During inflammation, neutrophils that infiltrate lung tissue undergo NET formation that results in the production of ROS and pro-inflammatory cytokines. This process plays a central role in the development of lung injury. [102]

NOD-like receptor signaling pathway

NOD-like receptors are one type of pattern recognition receptors. [97] NOD-like receptors are involved in innate immunity by detecting DAMPs that are associated with cellular stress (e.g., radiation [103]) and intracellular PAMPs that enter the cell through phagocytosis as pattern recognition receptors. [104] Subsequently, these intracellular receptors activate the MAPK and NF-kappa B pathways; [104] secrete numerous pro-inflammatory cytokines; and induce neutrophil influx into the lungs. [97, 105] In a murine lung injury model, [106] perturbations in the NOD-like receptor and p38 MAPK pathways were found during plateau hypoxia exposure.

Chemokine signaling pathway

Chemokines are chemotactic cytokines that control the movement of circulating immune cells by mediating cell-to-cell communication. [107] The interactions between chemokines and

their receptors lead to the activation of intracellular signaling and subsequent chemotactic migration of lymphocytes into inflamed lung tissue. [107] Infiltration of inflammatory and immune cells in lung tissues is the main pathogenic characteristic of a number of pulmonary diseases (e.g., cystic fibrosis, [108] interstitial lung disease, [109] lung adenocarcinoma, [110] pulmonary fibrosis, [111] acute lung injury [112]). Taken together, dysregulation of chemokine signaling in the lungs induces inflammation and progressive lung damage [107, 108] and may contribute to the occurrence of dyspnea.

Signal Molecules and Interaction

Signal molecules transmit information between the cells of multicellular organisms. [113] These molecules act as ligands that bind to receptors on target cells. [113] In this analysis, cytokine-cytokine receptor interaction pathway was associated with shortness of breath.

Cytokine-cytokine receptor interaction

Cytokines are the most common signal molecules that act as intercellular messengers and mediate cell growth, differentiation, and apoptosis. [114] While no studies were identified that reported that cytokines directly activate sensory neurons in airways, cytokine-cytokine receptor interactions in the lungs play an important role in tissue repair in response to lung injury and/or infection. [79] Evidence suggests that the dysregulation of cytokine production leads to profound lung injury, remodeling, and consequently fibrosis, [79] that may result in shortness of breath.

Cell Growth and Death

Cell proliferation and death are regulated to maintain tissue homeostasis. [115] In this analysis, the cell growth and death pathways that were identified included: apoptosis, necroptosis, and cell senescence. Among these pathways, the apoptosis pathway had the highest closeness score.

Apoptosis pathway

Apoptosis plays a primary role in the maintenance of balance between cell growth and death. Lung epithelial cell apoptosis is an initial and primary event in response to lung damage in a variety of lung diseases. [116, 117] Recruited or resident macrophages within the lung induce apoptosis in response to cellular or mechanical stress, epithelial injury, exposure to damaging particles or toxic molecules (e.g., chemotherapy), and/or infectious agents. [118] While apoptosis is a regulated cell death mechanism that eliminates unwanted cells, [115] failure to remove apoptotic cells by phagocytes leads to release of ROS and DAMPs that can induce epithelial and endothelial dysfunction. [116, 117] Given that the prolongation of inflammation and the delay in repair processes leads to lung damage and irreversible lung remodeling, perturbation in apoptosis may contribute to the development and persistence of dyspnea.

Overlapping Mechanisms

Of the 29 inflammatory pathways listed on Table 4, 14 of them were identified to be members for the five respiratory disease-related pathways listed in Table 6. Of note, the JAK-STAT signaling, MAPK signaling, apoptosis, and NOD-like receptor signaling pathways were found across at least three respiratory conditions. While these preliminary results need to be interpreted with caution, the relatively high prevalence rates for shortness of breath in these respiratory conditions (e.g., 49% in patients three months following COVID-19, [119] 59.3% in influenza A, [120] 11% in asthma [121]) support the hypothesis that common inflammatory mechanisms contribute to the occurrence of this symptom. Future studies need to identify distinct shortness of breath profiles in patients with common respiratory conditions and evaluate for perturbations in inflammatory pathways.

LIMITATIONS

First, given that this study is the first to report on associations between shortness of breath and pathway perturbations, these findings warrant confirmation. Second, because

patients were assessed during chemotherapy, future research needs to evaluate shortness of breath and molecular mechanisms associated with other treatments. Longitudinal studies are needed that assess for associations between changes in multiple dimensions of shortness of breath (i.e., severity, distress) and changes in gene expression and pathway perturbations.

CONCLUSIONS

This study is the first to identify associations between shortness of breath and a number of inflammatory pathways and the interconnections among these pathways. While our findings warrant confirmation, we hypothesize that the mechanisms that underlie dyspnea in oncology patients may be similar to other respiratory diseases. Comparative studies across various diseases with dyspnea as a major symptom would allow for the identification of common and distinct mechanisms for this symptom. In addition, inflammatory pathways associated with shortness of breath can be triggered by various stimuli (e.g., tumor cells, chemotherapy, pulmonary infection, air pollutants, psychological stress). Future studies need to examine the mechanisms that underlie the relationship between dyspnea and various triggers. Lastly, research that utilizes lung tissues (e.g., sputum) may allow the identification of local effects of inflammatory pathways in the development of dyspnea in patients with cancer.

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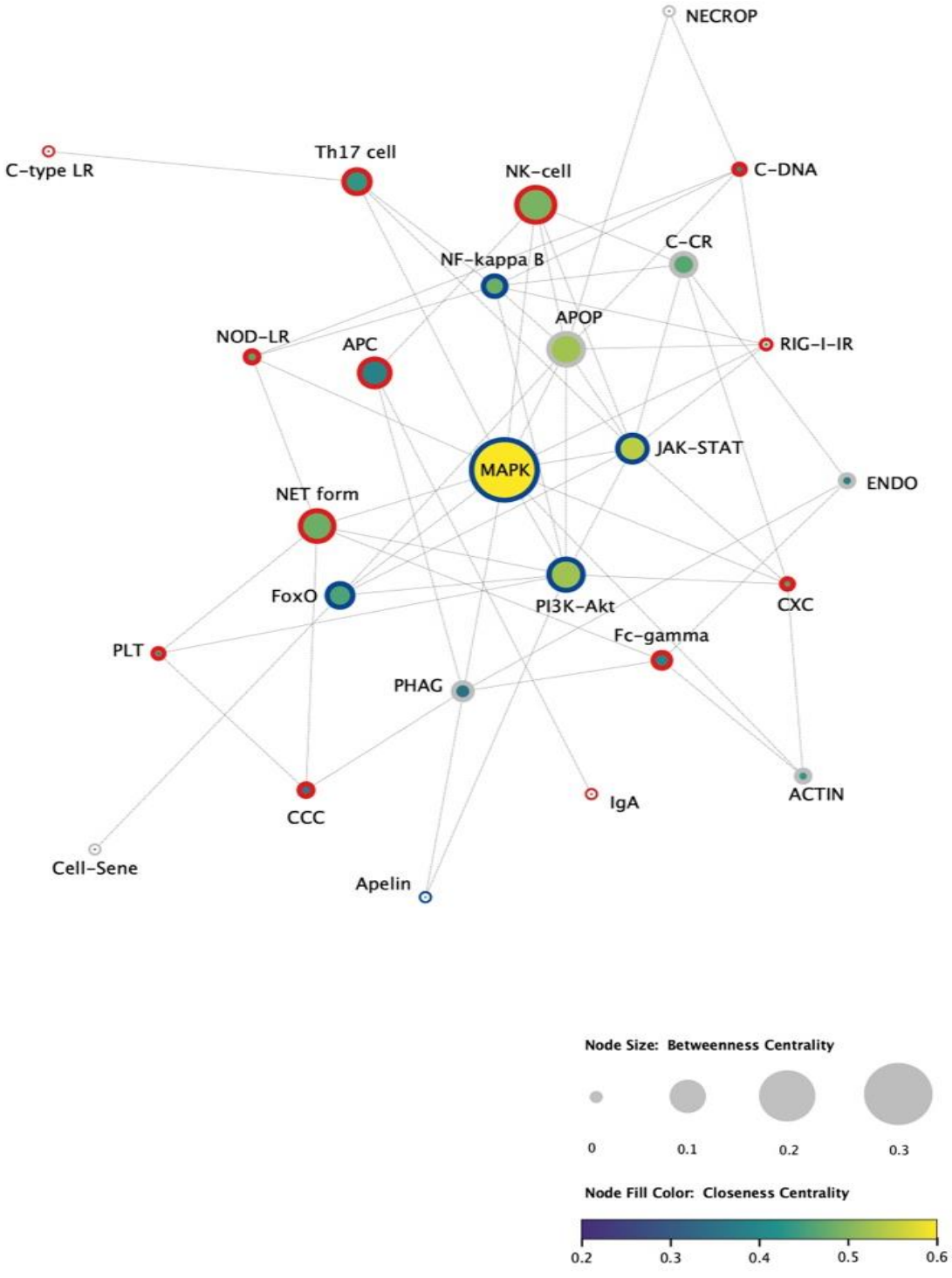
NECROP
C-type LR
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NK-cell
C-DNA
C-CR
NF-kappa B
APOP
NOD-LR
APC
RIG-I-IR
JAK-STAT
MAPK
ENDO
NET form
FoxO
PI3K-Akt
CXC
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Cell-Sene
Apelin
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Figure 6.1. An Undirected Shortness of Breath Knowledge Network generated from connections among the perturbed of inflammation-related Kyoto Encyclopedia of Genes and Genomes (KEGG) signaling pathways associated with Shortness of Breath in Patients receiving chemotherapy. Nodes represent each of the KEGG signaling pathways. Edges represent connections between the pathways. Node size corresponds to betweenness centrality score (bigger is higher). Node fill shade corresponds to closeness centrality score (yellowish is higher). Node border color represents KEGG Ontology classification (i.e., blue = signal transduction; red = immune system; grey = others). Abbreviations: ACTIN = regulation of actin cytoskeleton; APC = antigen processing and presentation; Apelin = apelin signaling pathway; APOP = apoptosis; CCC = complement and coagulation cascades; C-CR = cytokine-cytokine receptor interaction; C-DNA = cytosolic DNA-sensing pathway; Cell-Sene = cellular senescence; C-type LR = C-type lectin receptor signaling pathway; CXC = chemokine signaling pathway; ENDO = endocytosis; Fc-gamma = Fc gamma R-mediated phagocytosis; FoxO = FoxO signaling pathway; IgA = intestinal immune network for IgA production; JAK-STAT = JAK-STAT signaling pathway; MAPK = MAPK signaling pathway; NECROP = necroptosis; NET form = neutrophil extracellular trap formation; NF-kappa B = NF-kappa B signaling pathway; NK-cell = natural killer cell mediated cytotoxicity; NOD-LR = NOD-like receptor signaling pathway; PHAG = phagosome; PI3K-Akt = PI3K-Akt signaling pathway; PLT = platelet activation; RIG-I-IR = RIG-I-like receptor signaling pathway; Th17 cell = Th17 cell differentiation.

Table 6.1. Differences in Demographic and Clinical Characteristics at Enrollment Between Patients in the None versus the High Shortness of Breath Classes in the RNA seq Sample

Characteristic	None (0) 79.5% (n = 233)	High (1) 20.5% (n = 60)	Statistics
	Mean (SD)	Mean (SD)	
Age (years)	56.7 (12.1)	59.3 (11.1)	t = -1.51, p = 0.132
Education (years)	16.0 (3.0)	16.3 (3.4)	t = -0.72, p = 0.470
Body mass index (kg/m^2)	25.7 (5.1)	26.9 (6.1)	t = -1.48, p = 0.139
Karnofsky Performance Status score	79.0 (12.2)	73.6 (13.1)	t = 2.99, p = 0.003
Number of comorbidities	2.4 (1.4)	3.1 (1.8)	t = -3.39, p = 0.001
Self-administered Comorbidity Questionnaire score	5.4 (3.0)	7.1 (4.4)	t = -3.64, p < 0.001
Alcohol Use Disorders Identification Test score	3.1 (2.2)	2.3 (1.2)	t = 2.55, p = 0.011
Time since diagnosis (years)	1.6 (3.1)	1.8 (2.8)	U, p = 0.343
Time since diagnosis (years, median)	0.43	0.47	
Number of prior cancer treatments	1.4 (1.3)	1.7 (1.7)	t = -1.26, p = 0.207
Number of metastatic sites including lymph node involvement	1.2 (1.2)	1.3 (1.4)	t = -0.10, p = 0.921
Number of metastatic sites excluding lymph node involvement	0.8 (1.0)	0.9 (1.2)	t = -0.62, p = 0.533
Hemoglobin (g/dL)	11.6 (1.4)	11.1 (1.4)	t = 2.48, p = 0.014
Hematocrit (%)	34.7 (3.8)	33.4 (4.4)	t = 2.32, p = 0.021
MAX2 score	0.18 (0.08)	0.19 (0.08)	t = -0.78, p = 0.434
	% (n)	% (n)	
Gender Female Male	 75.5 (176) 24.5 (57)	 83.3 (50) 16.7 (10)	FE, p = 0.230
Ethnicity White Black Asian or Pacific Islander Hispanic mixed or other	 65.2 (152) 7.7 (18) 17.6 (41) 9.4 (22)	 76.7 (46) 6.7 (2) 3.3 (4) 13.3 (8)	X^2 = 6.69; p = 0.083
Married or partnered (% yes)	65.7 (153)	53.3 (32)	FE, p = 0.098
Lives alone (% yes)	21.0 (49)	28.3 (17)	FE, p = 0.229
Childcare responsibilities (% yes)	21.9 (51)	13.3 (8)	FE, p = 0.153
Adult care responsibilities (% yes)	6.9 (16)	6.7 (4)	FE, p = 1.000
History of premature birth (% yes)	4.7 (11)	6.7 (4)	FE, p = 0.518
Currently employed (% yes)	36.9 (86)	28.3 (17)	FE, p = 0.229

Table 6.1. Differences in Demographic and Clinical Characteristics at Enrollment Between Patients in the None versus the High Shortness of Breath Classes in the RNA seq Sample

Characteristic	None (0) 79.5% (n = 233)	High (1) 20.5% (n = 60)	Statistics
	Mean (SD)	Mean (SD)	
Income			
<$30,000	16.3 (38)	31.7 (19)	
$30,000 to <$70,000	23.2 (54)	13.3 (8)	U, p = 0.171
$70,000 to <$100,000	21.5 (50)	20.0 (12)	
≥$100,000	39.1 (91)	35.0 (21)	
Specific comorbidities (% yes)			
Heart disease	4.7 (11)	15.0 (9)	FE, p = 0.009
High blood pressure	34.3 (80)	30.0 (18)	FE, p = 0.646
Lung disease	6.0 (14)	26.7 (16)	FE, p < 0.001
Diabetes	11.2 (26)	11.7 (7)	FE, p = 1.000
Ulcer or stomach disease	4.3 (10)	3.3 (2)	FE, p = 1.000
Kidney disease	1.0 (2)	0.0 (0)	n/a
Liver disease	8.2 (19)	3.3 (2)	FE, p = 0.267
Anemia or blood disease	7.7 (18)	18.3 (11)	FE, p = 0.026
Depression	15.9 (37)	31.7 (19)	FE, p = 0.009
Osteoarthritis	11.2 (26)	15.0 (9)	FE, p = 0.382
Back pain	29.2 (68)	40.0 (24)	FE, p = 0.120
Rheumatoid arthritis	30.0 (7)	13.3 (8)	FE, p = 0.004
Exercise on a regular basis (% yes)	69.1 (161)	63.3 (38)	FE, p = 0.439
Smoking current or history of (% yes)	32.6 (76)	43.3 (26)	FE, p = 0.130
Cancer diagnosis			X^2 = 27.39, p < 0.001
Breast	39.1 (91)	41.7 (25)	NS
Gastrointestinal	40.8 (95)	21.7 (13)	0 > 1
Gynecological	15.5 (36)	11.7 (7)	NS
Lung	4.7 (11)	25.0 (15)	0 < 1
Lung metastasis (% yes)	9.4 (22)	18.3 (11)	FE, p = 0.066
Type of prior cancer treatment			
No prior treatment	27.0 (63)	30.0 (18)	X^2 = 3.39, p = 0.335
Only surgery, CTX, or RT	44.2 (103)	38.3 (23)	
Surgery & CTX, or surgery & RT, or CTX & RT	18.0 (42)	13.3 (8)	
Surgery & CTX & RT	10.7 (25)	18.3 (11)	
CTX cycle length			
14 day cycle	50.2 (117)	35.0 (21)	U, p = 0.030
21 day cycle	42.5 (99)	53.3 (32)	0 < 1
28 day cycle	7.3 (17)	11.7 (7)	
Emetogenicity of CTX			
Minimal/low	15.0 (35)	25.0 (15)	U, p = 0.531
Moderate	67.8 (158)	53.3 (32)	
High	17.2 (40)	21.7 (13)	
Antiemetic regimens			X^2=11.49, p=0.009
None	3.9 (9)	13.3 (8)	0 < 1
Steroid alone or serotonin receptor antagonist alone	18.0 (42)	15.0 (9)	NS
Serotonin receptor antagonist and steroid	52.4 (122)	36.7 (22)	0 > 1
NK-1 receptor antagonist and two other antiemetics	25.8 (60)	35.0 (21)	NS

Table 6.1. Differences in Demographic and Clinical Characteristics at Enrollment Between Patients in the None versus the High Shortness of Breath Classes in the RNA seq Sample

Abbreviations: CTX = chemotherapy; FE = Fisher's exact test; g/dL = grams per deciliter; kg = kilograms; m^2 = meter squared; n/a = not applicable; NK-1 = neurokinin-1; NS = not significant; RNA = ribonucleic acid; RT = radiation therapy; SD = standard deviation; U = Mann-Whitney U test

Table 6.2. Differences in Demographic and Clinical Characteristics at Enrollment Between Patients in the None versus the High Shortness of Breath Classes in the Microarray Sample

Characteristic	None (0) 82.0% (n = 242)	High (1) 18.0% (n = 53)	Statistics
	Mean (SD)	Mean (SD)	
Age (years)	56.8 (11.4)	57.5 (13.2)	t = -0.38, p = 0.705
Education (years)	16.4 (3.0)	16.2 (2.9)	t = 0.63, p = 0.531
Body mass index (kg/m^2)	26.5 (5.8)	27.1 (7.3)	t = -0.68, p = 0.498
Karnofsky Performance Status score	80.8 (11.2)	77.3 (11.3)	t = 2.10, p = 0.037
Number of comorbidities	2.3 (1.3)	3.1 (1.4)	t = -4.03, p < 0.001
Self-administered Comorbidity Questionnaire score	5.2 (2.7)	7.0 (3.3)	t = -4.08, p < 0.001
Alcohol Use Disorders Identification Test score	2.9 (2.2)	3.1 (2.7)	t = -0.61, p = 0.542
Time since diagnosis (years)	1.9 (3.3)	2.7 (4.2)	U, p = 0.182
Time since diagnosis (years, median)	0.42	0.79	
Number of prior cancer treatments	1.6 (1.5)	2.2 (1.9)	t = -2.15, p = 0.032
Number of metastatic sites including lymph node involvement	1.2 (1.2)	1.4 (1.4)	t = -0.87, p = 0.384
Number of metastatic sites excluding lymph node involvement	0.8 (1.1)	0.9 (1.2)	t = -0.88, p = 0.381
Hemoglobin (g/dL)	11.9 (1.4)	11.6 (1.3)	t = 1.32, p = 0.188
Hematocrit (%)	35.2 (4.0)	34.3 (3.9)	t = 1.49, p = 0.136
MAX2 score	0.17 (0.08)	0.18 (0.08)	t = -0.87, p = 0.387
	% (n)	% (n)	
Gender			
Female	77.3 (187)	86.8 (46)	FE, p = 0.140
Male	22.7 (55)	13.2 (7)	
Ethnicity			
White	69.8 (169)	71.7 (38)	X^2 = 0.58, p = 0.901
Black	5.8 (14)	11.3 (4)	
Asian or Pacific Islander	12.0 (29)	7.5 (6)	
Hispanic mixed or other	12.4 (30)	9.4 (5)	
Married or partnered (% yes)	69.8 (169)	62.3 (33)	FE, p = 0.328
Lives alone (% yes)	16.9 (41)	28.3 (15)	FE, p = 0.080
Childcare responsibilities (% yes)	24.4 (59)	24.5 (13)	FE, p = 1.000
Adult care responsibilities (% yes)	7.9 (19)	7.5 (4)	FE, p = 1.000
History of premature birth (% yes)	5.4 (13)	5.7 (3)	FE, p = 1.000
Currently employed (% yes)	34.7 (84)	28.3 (15)	FE, p = 0.424
Income			
<$30,000	16.5 (40)	28.3 (15)	U, p = 0.005 0 < 1
$30,000 to <$70,000	18.6 (45)	26.4 (14)	
$70,000 to <$100,000	16.5 (40)	18.9 (10)	
≥$100,000	48.3 (117)	26.4 (14)	

Table 6.2. Differences in Demographic and Clinical Characteristics at Enrollment Between Patients in the None versus the High Shortness of Breath Classes in the Microarray Sample

Characteristic	None (0) 82.0% (n = 242)	High (1) 18.0% (n = 53)	Statistics
	Mean (SD)	Mean (SD)	
Specific comorbidities (% yes)			
Heart disease	6.2 (15)	5.7 (3)	FE, p = 1.000
High blood pressure	28.5 (69)	34.0 (18)	FE, p = 0.506
Lung disease	7.4 (18)	26.4 (14)	FE, p < 0.001
Diabetes	5.8 (14)	9.4 (5)	FE, p = 0.353
Ulcer or stomach disease	4.5 (11)	7.5 (4)	FE, p = 0.321
Kidney disease	0.4 (1)	1.9 (1)	FE, p = 0.328
Liver disease	5.0 (12)	11.3 (6)	FE, p = 0.107
Anemia or blood disease	13.6 (33)	9.4 (5)	FE, p = 0.502
Depression	18.6 (45)	35.8 (19)	FE, p = 0.009
Osteoarthritis	11.2 (27)	24.5 (13)	FE, p = 0.015
Back pain	21.9 (53)	37.7 (20)	FE, p = 0.022
Rheumatoid arthritis	4.5 (11)	5.7 (3)	FE, p = 0.723
Exercise on a regular basis (% yes)	70.7 (171)	67.9 (36)	FE, p = 0.741
Smoking current or history of (% yes)	35.1 (85)	37.7 (20)	FE, p = 0.753
Cancer diagnosis			X^2=13.55, p=0.004
Breast	35.1 (85)	37.7 (20)	NS
Gastrointestinal	29.8 (72)	11.3 (6)	0 > 1
Gynecological	24.4 (59)	24.5 (13)	NS
Lung	10.7 (26)	26.4 (14)	0 < 1
Lung metastasis (% yes)	8.7 (21)	18.9 (10)	FE, p = 0.044
Type of prior cancer treatment			
No prior treatment	19.4 (47)	20.8 (11)	X^2 = 3.48, p = 0.323
Only surgery, CTX, or RT	46.7 (113)	34.0 (18)	
Surgery & CTX, or surgery & RT, or CTX & RT	20.2 (49)	24.5 (13)	
Surgery & CTX & RT	13.6 (33)	20.8 (11)	
CTX cycle length			
14 day cycle	37.2 (90)	17.0 (9)	U, p = 0.012
21 day cycle	55.8 (135)	75.5 (40)	0 < 1
28 day cycle	7.0 (17)	7.5 (4)	
Emetogenicity of CTX			
Minimal/low	20.2 (49)	20.8 (11)	U, p = 0.769
Moderate	62.4 (151)	64.2 (34)	
High	17.4 (42)	15.1 (8)	
Antiemetic regimens			X^2 = 3.55, p = 0.314
None	10.7 (26)	3.8 (2)	
Steroid alone or serotonin receptor antagonist alone	20.7 (50)	28.3 (15)	
Serotonin receptor antagonist and steroid	47.1 (114)	49.1 (26)	
NK-1 receptor antagonist and two other antiemetics	21.5 (52)	18.9 (10)	

Abbreviations: CTX = chemotherapy; dL = deciliter; FE = Fisher's exact test; g = grams; kg = kilograms; m^2 = meter squared; NK-1 = neurokinin-1; NS = not significant; RNA = ribonucleic acid; RT = radiation therapy; SD = standard deviation; U = Mann-Whitney U test

Table 6.3. Multiple Logistic Regression Analyses Predicting Membership in the High Shortness of Breath Class

RNA seq Sample (n = 293)			
Predictors	Odds Ratio	95% CI	p-value
Karnofsky Performance Status score	0.97	0.95, 1.00	0.041
Hemoglobin (g/dL)	0.83	0.65, 1.05	0.122
Cancer diagnosis			
Breast	1.00		
Gastrointestinal	0.59	0.27, 1.23	0.168
Gynecological	0.69	0.25, 1.68	0.429
Lung	4.72	1.90, 12.11	0.001
Overall model fit: AUC of the ROC = 0.713			
Microarray Sample (n = 295)			
Predictors	Odds Ratio	95% CI	p-value
Karnofsky Performance Status score	0.98	0.95, 1.01	0.148
Self-Administered Comorbidity Questionnaire score	1.18	1.07, 1.31	0.002
Cancer diagnosis			
Breast	1.00		
Gastrointestinal	0.33	0.11, 0.84	0.028
Gynecological	0.92	0.41, 2.03	0.842
Lung	1.74	0.73, 4.09	0.204
Overall model fit: AUC of the ROC = 0.713			

Abbreviations: AUC = area under curve; CI = confidence interval; g/dL= grams per deciliter; RNA = ribonucleic acid; ROC = receiver operating characteristic

Table 6.4. Perturbed Inflammatory KEGG Signaling Pathways Between Patients in the None Versus the High Shortness of Breath Classes

Pathway ID	Pathway Name	Combined Analysis Statistics
Immune System		
hsa04612	Antigen processing and presentation	$X^2 = 21.97$, pPert = 0.0042
hsa04672	Intestinal immune network for IgA production	$X^2 = 21.94$, pPert = 0.0042
hsa04610	Complement and coagulation cascades	$X^2 = 20.64$, pPert = 0.0064
hsa04613	Neutrophil extracellular trap formation	$X^2 = 19.19$, pPert = 0.0077
hsa04621	NOD-like receptor signaling	$X^2 = 18.84$, pPert = 0.0077
hsa04650	Natural killer cell mediated cytotoxicity	$X^2 = 16.94$, pPert = 0.0119
hsa04623	Cytosolic DNA-sensing pathway	$X^2 = 16.55$, pPert = 0.0125
hsa04625	C-type lectin receptor signaling pathway	$X^2 = 15.72$, pPert = 0.0149
hsa04622	RIG-I-like receptor signaling pathway	$X^2 = 15.66$, pPert = 0.0150
hsa04062	Chemokine signaling pathway	$X^2 = 15.51$, pPert = 0.0157
hsa04659	Th17 cell differentiation	$X^2 = 14.64$, pPert = 0.0199
hsa04666	Fc gamma R-mediated phagocytosis	$X^2 = 14.23$, pPert = 0.0220
hsa04611	Platelet activation	$X^2 = 13.75$, pPert = 0.0248
Signal Molecules and Interaction		
hsa04060	Cytokine-cytokine receptor interaction	$X^2 = 22.75$, pPert = 0.0042
hsa04061	Viral protein interaction with cytokine and cytokine receptor	$X^2 = 19.04$, pPert = 0.0077
Signal Transduction		
hsa04151	PI3K-Akt signaling pathway	$X^2 = 16.17$, pPert = 0.0137
hsa04010	MAPK signaling pathway	$X^2 = 16.14$, pPert = 0.0137
hsa04371	Apelin signaling pathway	$X^2 = 15.35$, pPert = 0.0163
hsa04068	FoxO signaling pathway	$X^2 = 14.80$, pPert = 0.0191
hsa04390	Hippo signaling pathway	$X^2 = 14.50$, pPert = 0.0203
hsa04064	NF-kappa B signaling pathway	$X^2 = 13.87$, pPert = 0.0242
hsa04630	JAK-STAT signaling pathway	$X^2 = 13.77$, pPert = 0.0248
Transport and Catabolism		
hsa04144	Endocytosis	$X^2 = 19.50$, pPert = 0.0077
hsa04145	Phagosome	$X^2 = 16.78$, pPert = 0.0125
hsa04146	Peroxisome	$X^2 = 15.18$, pPert = 0.0169
Cell growth and death		
hsa04210	Apoptosis	$X^2 = 19.42$, pPert = 0.0077
hsa04217	Necroptosis	$X^2 = 18.73$, pPert = 0.0077
hsa04218	Cellular senescence	$X^2 = 16.54$, pPert = 0.0125
Cell motility		
hsa04810	Regulation of actin cytoskeleton	$X^2 = 15.19$, pPert = 0.0169

Table 6.4. Perturbed Inflammatory KEGG Signaling Pathways Between Patients in the None Versus the High Shortness of Breath Classes

Abbreviations: DNA = deoxyribonucleic acid; FoxO = Forkhead box O; ID = identifier; IgA = Immunoglobulin A; JAK-STAT = Janus Kinase/Signal Transducers and Activators of Transcription; KEGG = Kyoto Encyclopedia of Genes and Genomes; MAPK = mitogen-activated protein kinase; NF-kappa B = nuclear factor kappa light chain enhancer of activated B cells; NOD = nucleotide-binding and Oligomerization Domain; pPert = combined perturbation *p*-value using Fisher's Method adjusted using the Bonferroni method; PI3K-Akt = Phosphatidylinositol-3-kinase-protein kinase B; R = Receptor; RIG-I = Retinoic acid-inducible gene-I-like receptors; Th17 = T-helper 17.

Table 6.5. Centrality Measures for the Perturbed Inflammatory KEGG Signaling Pathway Shortness of Breath Knowledge Network

Pathway ID	KO classification	Pathway Name	Betweenness Centrality	Closeness Centrality*	Degree Centrality†
hsa04010	Signal transduction	**MAPK signaling pathway**	**0.261**	**0.610**	**0.480**
hsa04630	Signal transduction	**JAK-STAT signaling pathway**	0.097	**0.556**	0.200
hsa04210	Cell growth and death	**Apoptosis**	0.120	**0.532**	0.360
hsa04151	Signal transduction	**PI3K-Akt signaling pathway**	0.118	**0.532**	0.360
hsa04650	Immune system	**Natural killer cell mediated cytotoxicity**	0.135	**0.500**	0.240
hsa04613	Immune system	**Neutrophil extracellular trap formation**	0.115	**0.490**	0.120
hsa04064	Signal transduction	**NF-kappa B signaling pathway**	0.065	**0.490**	0.360
hsa04060	Signal molecules and interaction	**Cytokine-cytokine receptor interaction**	0.073	**0.472**	0.160
hsa04621	Immune system	**NOD-like receptor signaling pathway**	0.024	**0.472**	0.200
hsa04068	Signal transduction	**FoxO signaling pathway**	0.080	**0.463**	0.200
hsa04062	Immune system	**Chemokine signaling pathway**	0.017	**0.463**	0.280
hsa04622	Immune system	RIG-I-like receptor signaling pathway	0.007	0.446	0.160
hsa04659	Immune system	Th17 cell differentiation	0.082	0.439	0.160
hsa04810	Cell motility	Regulation of actin cytoskeleton	0.023	0.439	0.120
hsa04623	Immune system	Cytosolic DNA-sensing pathway	0.015	0.424	0.160
hsa04611	Immune system	Platelet activation	0.013	0.410	0.120
hsa04666	Immune system	Fc gamma R-mediated phagocytosis	0.042	0.403	0.120
hsa04371	Signal transduction	Apelin signaling pathway	0.000	0.403	0.200
hsa04612	Immune system	Antigen processing and presentation	0.101	0.391	0.200
hsa04144	Transport and catabolism	Endocytosis	0.024	0.385	0.120
hsa04610	Immune system	Complement and coagulation cascades	0.026	0.379	0.200
hsa04271	Cell growth and death	Necroptosis	0.000	0.362	0.080
hsa04145	Transport and catabolism	Phagosome	0.048	0.352	0.040
hsa04218	Cell growth and death	Cellular senescence	0.000	0.321	0.040
hsa04625	Immune system	C-type lectin receptor signaling pathway	0.000	0.309	0.080

Table 6.5. Centrality Measures for the Perturbed Inflammatory KEGG Signaling Pathway Shortness of Breath Knowledge Network

Pathway ID	KO classification	Pathway Name	Betweenness Centrality	Closeness Centrality*	Degree Centrality†
hsa04672	Immune system	Intestinal immune network for IgA production	0.000	0.284	0.040

Abbreviations: DNA = Deoxyribonucleic acid; FoxO = Forkhead box O; hsa = Homo sapiens; ID = identifier; IgA = Immunoglobulin A; JAK-STAT = Janus Kinase/Signal Transducers and Activators of Transcription; KEGG = Kyoto Encyclopedia of Genes and Genomes; KO = Kyoto Encyclopedia of Genes and Genomes Orthology; MAPK = mitogen-activated protein kinase; NF-kappa B = nuclear factor kappa light chain enhancer of activated B cells; NOD = nucleotide-binding and oligomerization domain; PI3K-Akt = phosphatidylinositol-3-kinase-protein kinase B; R = receptor; RIG-I = Retinoic acid-inducible gene-I-like receptors; Th17 = T-helper 17

*Table organized in descending order for closeness measures
†Degree centrality = degree / (total number of nodes - 1)

Table 6.6. Perturbed Respiratory Disease-Related KEGG Signaling Pathways Between Patients in the None Versus the High Shortness of Breath Classes

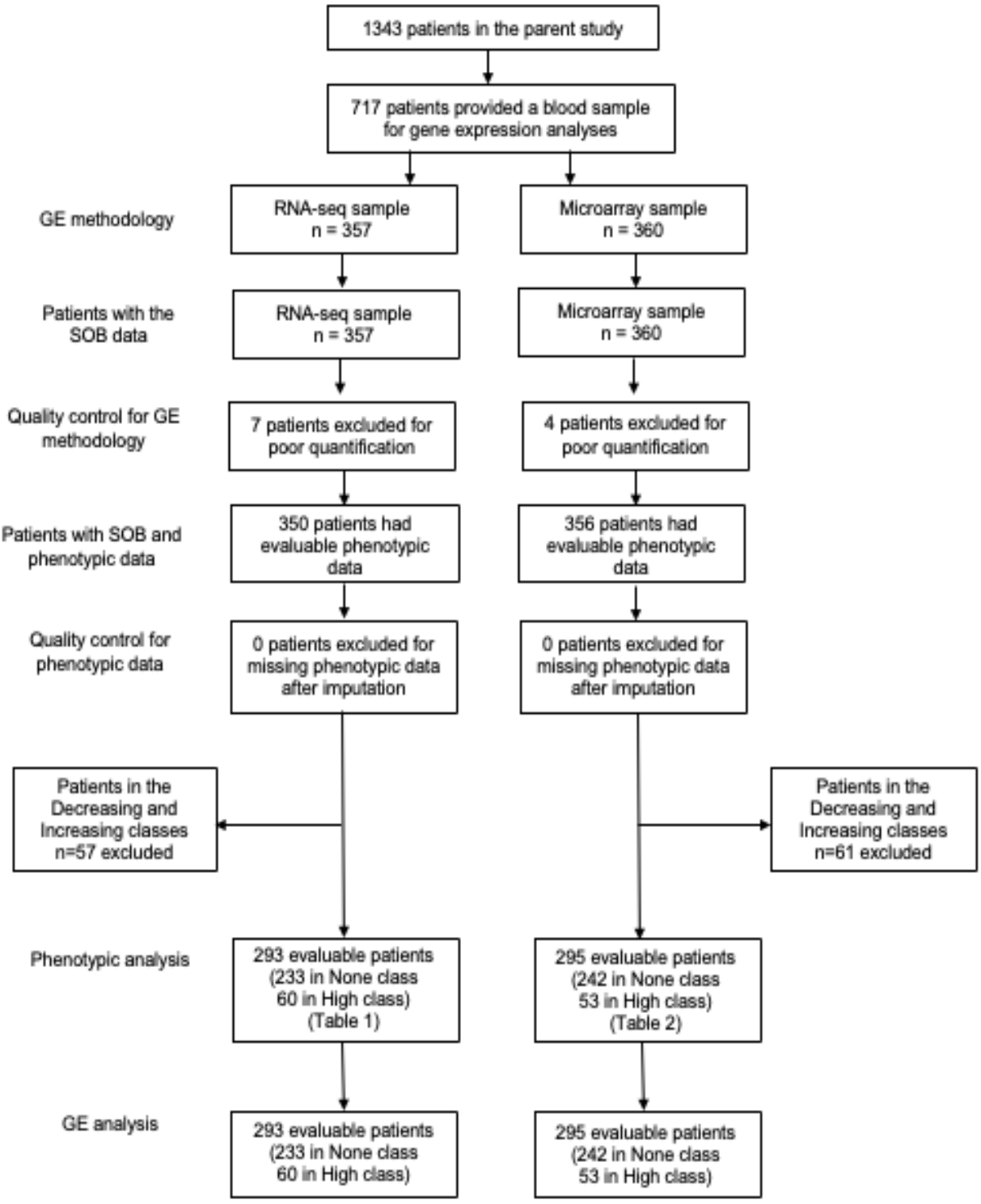
Pathway ID	Pathway Name	Combined Analysis Statistics
Infectious Disease; Viral		
hsa05171	Coronavirus disease –COVID-19	$X^2 = 30.41$, pPert = 0.0009
hsa05164	Influenza A	$X^2 = 22.98$, pPert = 0.0042
Infectious Disease; Bacterial		
hsa05133	Pertussis	$X^2 = 19.40$, pPert = 0.0077
hsa05152	Tuberculosis	$X^2 = 15.87$, pPert = 0.0145
Immune Disease		
hsa05310	Asthma	$X^2 = 18.66$, pPert = 0.0077

Abbreviations: COVID-19 = coronavirus disease; ID = identifier; KEGG = Kyoto Encyclopedia of Genes and Genomes; pPert = combined perturbation *p*-value using Fisher's Method adjusted using the Bonferroni method

Table 6.7. Overlap of Significantly Perturbed Inflammatory and Common Respiratory Disease Pathways associated with the Occurrence of Dyspnea in Patients Receiving Chemotherapy.

Inflammatory-related KEGG Pathways	**Common Respiratory Disease KEGG Pathways**				
	COVID-19 pathway	Influenza A pathway	Tuberculosis pathway	Pertussis pathway	Asthma pathway
JAK-STAT signaling pathway	x	x	x		x
NOD-like receptor signaling pathway	x	x	x		
MAPK signaling pathway		x	x	x	
Apoptosis		x	x	x	
Antigen processing and presentation			x		x
Endocytosis	x	x			
RIG-I-like receptor signaling pathway	x	x			
Natural killer cell mediated cytotoxicity	x				
Cytosolic DNA-sensing pathway	x				
Fc gamma R-mediated phagocytosis	x				
Complement and coagulation cascades	x			x	
Platelet activation	x				
Neutrophil extracellular trap formation	x				
Cytokine-cytokine receptor interaction					x

Abbreviations: DNA = deoxyribonucleic acid, JAK-STAT = Janus Kinase/Signal Transducers and Activators of Transcription, KEGG = Kyoto Encyclopedia of Genes and Genomes, MAPK = mitogen-activated protein kinase, NOD = nucleotide-binding and oligomerization domain, RIG-I = Retinoic acid-inducible gene-I-like receptors



Supplementary Figure 1: Flow diagram of the number of patients available for phenotypic and GE analyses for SOB

Abbreviations: GE = gene expression; RNA-seq = ribonucleic acid sequencing; SOB = shortness of breath

Chapter 7

Conclusions, Implications for Clinical Practice, and Directions for Future Research

CONCLUSIONS

The purposes of this dissertation research were to: 1) create a conceptual model of various risk factors for dyspnea in patients with cancer (i.e., the Multifactorial Model of Dyspnea in Patients with Cancer [1]) and suggest plausible mechanisms for dyspnea based on the factors within the model; 2) conduct a systematic review of the literature on the occurrence and characteristics of dyspnea in oncology patients; 3) identify subgroups of patients with distinct shortness of breath profiles, evaluate for differences among these subgroups in demographic and clinical characteristics, three different dimensions of shortness of breath (i.e., severity, frequency, and distress), and quality of life outcomes; 4) evaluate for differences among these subgroups in levels of global, cancer-specific, and cumulative life stress and resilience, the occurrence rates for a number of SLEs, and the severity of common symptoms; and 5) evaluate for perturbed inflammatory pathways associated with the occurrence of shortness of breath in oncology patients receiving chemotherapy.

In Chapter One, limited evidence on phenotypic characteristics and molecular mechanisms of dyspnea were identified and served as areas of inquiry for this dissertation research. One gap in knowledge that delays the provision of timely symptom management for oncology patients with dyspnea is a limited understanding of the risk factors for this symptom. Another gap is the lack of information on the molecular mechanisms of shortness of breath. Given this lack of knowledge, additional studies are needed on the phenotypic characteristics of shortness of breath in oncology outpatients. In addition, while evidence suggests that association exists between dyspnea and inflammation, no studies have evaluated these relationships in oncology patients with shortness of breath. The subsequent chapters of this dissertation describe the findings regarding each of the stated purposes of this dissertation.

In Chapter Two, the Multifactorial Model of Dyspnea in Patients with Cancer was presented. [1] This conceptual model is an adaptation of the Mismatch Theory of Dyspnea for patients with cancer. The specific factors included in the model are: person (i.e., older age, male, lower socioeconomic status), clinical (i.e., smoking, cardiopulmonary disease), and cancer-related (e.g., lung cancer, cancer treatment(s)) factors, as well as respiratory muscle weakness (e.g., physical inactivity), co-occurring symptoms (e.g., anxiety, depression, fatigue, cough), stress, and resilience. In this paper, while the evidence to support each of the factors that contribute to dyspnea in patients with cancer is summarized, the large amount of inter-individual variability in this symptom across heterogeneous types of cancer suggested numerous areas for investigation. In addition, we acknowledged that progress in the management of this symptom would not be made until knowledge of its underlying mechanisms and associated risk factors were identified. Therefore, this paper concluded with recommendations for future research on phenotypic risk factors and molecular mechanisms.

Chapter Three reported the results of a systematic review of 117 studies that evaluated the characteristics of shortness of breath in patients with cancer receiving chemotherapy. This comprehensive review identified several conceptual and methodological limitations of dyspnea research in patients with cancer and provided recommendations for future research. First, a lack of consistency in the nomenclature for dyspnea was noted. While 63.2% of studies used the term dyspnea, 22.9% used breathlessness; 5.2% used shortness of breath; and one used difficulty breathing. This heterogeneity in the terms used for this symptom limited comparisons across studies. Second, the measures used to assess dyspnea were not multidimensional. Across the 117 studies, 94% of them evaluated only the intensity of dyspnea. Because only 14% of the studies evaluated risk factors associated with the severity of dyspnea, additional investigations were warranted to identify factors associated with the occurrence, distress, and impact of dyspnea. Third, patients with more severe dyspnea were more likely to report higher levels of other common symptoms (e.g., cough, pain, fatigue, depression, anxiety). Fourth, only

three mechanistic studies were identified that reported associations between dyspnea and candidate genes. Based on the findings from this systematic review, [2] we concluded that additional research is warranted on the phenotypic characteristics and molecular mechanisms of dyspnea warrants additional investigations.

In Chapter Four, we identified subgroups of patients (n=1338) with distinct shortness of breath profiles; evaluated for differences among these subgroups in demographic and clinical characteristics; the magnitude of other dimensions of shortness of breath (i.e., severity, frequency, distress), the severity of other common symptoms, and quality of life outcomes. The occurrence of shortness of breath was assessed using the Memorial Symptom Assessment Scale. [3] Latent class analysis was used to identify subgroups of patients with distinct shortness of breath profiles. Four distinct shortness of breath profiles were identified (None [70.5%], Decreasing [8.2%], Increasing [7.8%], High [13.5%]). Risk factors for membership in the High class included: a history of smoking, self-reported diagnosis of lung disease, having lung cancer, and receipt of a higher number of cancer treatments. In addition, compared to the Decreasing and Increasing classes, the High class's episodes of shortness of breath were more frequent and more severe. Compared to the None class, the High class reported poorer physical, psychological, and social functioning. This study provides new information on the occurrence, severity, distress for shortness of breath, the severity of co-occurring respiratory symptoms, and decrements in quality of life outcomes in a sample of patients with heterogenous types of cancer. In addition, a number of modifiable risk factors associated with shortness of breath (i.e., lower levels of physical functioning, depression, anemia) were identified.

Chapter Five built on the findings from Chapter Four. This study aimed to describe associations between shortness of breath and three types of stress, resilience, and common symptoms in a sample of oncology patients with heterogeneous types of cancer. Differences among the four subgroups of patients with distinct shortness of breath profiles (i.e., None [70.5%], Decreasing [8.2%], Increasing [7.8%], High [13.5%]) in levels of global, cancer-specific,

and cumulative life stress; levels of resilience; occurrence rates for stressful life events; and differences in the severity of common symptoms (i.e., trait and state anxiety, depressive symptoms, pain, sleep disturbance, morning and evening fatigue, morning and evening energy, and cognitive impairment) were evaluated. Compared to the None class, Decreasing and High classes had higher global and cancer-specific stress scores. The High class reported higher occurrence rates for several adverse childhood experiences. Compared to None class, Decreasing and High classes had higher depression, anxiety, and morning fatigue scores and lower morning energy and cognitive function scores. This study provided new information on the relationships between shortness of breath, stress, and other common symptoms. Research is needed to determine if multimodal interventions that include stress management, exercise training, and/or symptom management will decrease shortness of breath in oncology patients.

In Chapter Six, associations between the occurrence of dyspnea and perturbed inflammatory pathways were identified in patients receiving chemotherapy. Among 222 KEGG signaling pathways, 73 were significantly perturbed at a false discovery rate of 0.025. As shown in Table 6.4, 29 of these pathways were related to inflammatory mechanisms. While further validation studies are warranted, these findings suggest that activation of inflammatory pathways by cytotoxic drugs, tumor mass, and/or other types of cellular stress leads to the production of chemokines, cytokines, and oxidative stress. These processes may contribute to apoptosis of alveolar epithelial cells, alveolar epithelial cell injury, a decrease in cell migration in airway smooth muscle, and loss of the pulmonary endothelial barrier. During these remodeling processes in the lungs, we hypothesized that a variety of inflammatory mediators activate vagal afferent neurons in the airways that may result in the sensation of shortness of breath.

As part of this analysis, an unweighted knowledge network was created to identify the interactions between and among these perturbed inflammatory pathways. As shown in Figure 6.1, signal transduction pathways grouped together within the knowledge network. Subgroups of other inflammatory pathways were connected through these signal transduction pathways.

Among 26 inflammatory pathway nodes, the MAPK signaling pathway node had the highest closeness, betweenness, and degree centrality indices. These findings suggest that the MAPK signaling pathway may have the strongest “direct and indirect influence” and “local and global” effects within the dyspnea knowledge network.

In addition, in an exploratory analysis of the 73 pathways that met our FDR of 0.025, five of them were respiratory disease-related pathways (i.e., coronavirus disease, influenza A, pertussis, tuberculosis, asthma). An exploratory evaluation was done of the maps of these five respiratory disease-related pathways for inflammatory pathways. Of note, the JAK-STAT signaling, MAPK signaling, apoptosis, and NOD-like receptor signaling pathways were found across at least three of these five respiratory conditions. While these preliminary results warrant confirmation, the relatively high prevalence rates for shortness of breath in these respiratory conditions support the hypothesis that common inflammatory mechanisms contribute to the occurrence of this symptom.

IMPLICATIONS FOR CLINICAL PRACTICE

Findings from this dissertation research highlight that dyspnea contributes to the symptom burden of patients with cancer. Almost 30% of patients with heterogeneous types of cancer receiving chemotherapy reported shortness of breath. More importantly, 14% of these patients reported high occurrence rates for shortness of breath that persisted over their two cycles of chemotherapy (i.e., approximately 2 months). Two plausible explanations exist for these findings. First, clinicians did not assess for dyspnea during a routine clinical encounter and effective interventions were not prescribed. Alternatively, while clinicians did diagnose dyspnea and prescribed interventions, they were not effective. Several recommendations for clinical practice come from these findings.

Assessment

First and foremost, regardless of the type of cancer and its treatment(s), our findings suggest that clinicians need to assess for dyspnea routinely during clinical encounters. Given

the complexity of clinical care, clinicians could begin with an evaluation of the occurrence of dyspnea (i.e., yes or no). If patients report dyspnea, clinicians need to perform a comprehensive assessment of this symptom including: onset and duration; severity, distress, quality (e.g., what does it feel like?); aggravating and relieving factors; past or current treatment(s) and impact. In addition, they need to assess for common co-occurring symptoms (e.g., pain, depression, anxiety, cough) and their impact on the occurrence, severity, and distress of dyspnea. This type of assessment will guide the prescription of targeted interventions.

Interventions

Because no standard treatments for dyspnea are available, [4] careful consideration of the multiple factors associated with dyspnea is warranted to build targeted management plans that, if possible, treat the underlying cause. For example, patients with dyspnea from a large lung mass or malignant pleural effusion may benefit from medical or surgical interventions. For patients with co-occurring pulmonary and/or heart disease, oncology clinicians need to collaborate with the patient's primary care provider to optimize the management of these comorbidities.

In addition, the multidimensional domains of dyspnea warrant consideration during treatment planning. For example, patients may benefit from pulmonary rehabilitation programs if they report a deterioration in their functional status. [5] For patients with higher levels of distress from dyspnea, the use of psychological interventions (e.g., psychoeducation, stress management, relaxation therapy, resilience training) and the prescription of anxiolytics or antidepressants may help alleviate dyspnea. [4, 6] In terms of the association between dyspnea and inflammation, in several randomized controlled trials of patients with asthma, [7] chronic obstructive pulmonary disease, [8] and bronchiectasis, [9] pulmonary rehabilitation (e.g., exercise) helps decrease systemic inflammation. Studies on the efficacy of pulmonary rehabilitation to decrease dyspnea in oncology patients is warranted.

Evaluation

Once these interventions are initiated, ongoing assessments are warranted to evaluate their efficacy and make adjustments in order to optimize the management of dyspnea. The most current clinical guideline for dyspnea in patients with advanced cancer does not include specific recommendations that guide how to evaluate the efficacy of interventions. [4] Given the findings from our conceptual [1] and systematic review [2] papers, this evaluation needs to be performed based on the multidimensional domains of dyspnea.

RECOMMENDATIONS FOR FUTURE RESEARCH

Given that our studies are the first to evaluate for associations between a comprehensive list of demographic and clinical characteristics, as well as symptom severity scores, and levels of perceived stress and the occurrence of shortness of breath over two cycles of chemotherapy, [3, 10] future studies are warranted to confirm our findings. As listed in Table 2.1, numerous risk factors warrant additional evaluation to determine their relationship with dyspnea.

Our conceptual model [1] identified that very limited information is available on associations between a variety of social determinants of health and the occurrence, severity, and distress of dyspnea. Data from our studies suggest that higher occurrence rates of dyspnea were related to several social determinants (e.g., lower income, unemployment, older age, history of smoking, adverse childhood experience). [3, 10] Therefore, additional research is warranted that examines the relationship between additional social determinants of health (e.g., air pollution, neighborhood, physical environment, health insurance, food insecurity, social support) and the occurrence, severity, and distress of dyspnea.

In addition, future studies need to examine in more detail how various factors contribute to pulmonary toxicity in oncology patients. For example, in our study, [3] the receipt of a higher number of prior cancer treatment(s), as well as a past or current history of smoking, the presence of lung disease and/or lung cancer, were associated with higher occurrence rates of

dyspnea. Therefore, future studies are warranted that evaluate for changes in dyspnea trajectories in patients with different types of cancer and different types of treatment. When these studies are conducted, more detailed information needs to be collected on the co-occurrence of cardiopulmonary diseases, smoking history, and/or exposure to air pollutants or other toxic chemicals.

In terms of the multidimensionality of dyspnea, no studies were identified that evaluated for risk factors that increased the distress associated with dyspnea. Given that common and distinct mechanisms are involved in the sensory-perceptual and affective distress domains of dyspnea, studies need to identify distinct risk factors associated with the distress from dyspnea. In addition, additional studies are warranted that evaluate for the associations between a variety of types of stress and distress-related to dyspnea. These studies may provide new insights into the interrelationships between the hypothalamus and limbic system in augmenting distress from dyspnea. [11]

As identified in our systematic review, [2] dyspnea decreases patients' quality of life and functional exercise capacity. However, none of the studies examined mediating and/or moderating factors associated with these relationships. Future studies that identify specific mediators and moderators will enable researchers to develop and test more precise and targeted interventions for patients with dyspnea.

Multiple questions remain regarding the impact of common symptoms that co-occur with dyspnea. Regarding depression, some evidence suggests that dyspnea catastrophizing in patients with depression may increase their emotional responses to respiratory sensations. [12] In addition, a higher symptom burden and decreased physical conditioning in patients with depression appear to play a role in increasing dyspnea. [13] In a study of patients with advanced cancer, the administration of sertraline resulted in decreases in the severity of both depression and shortness of breath. Additional research is warranted on the efficacy of antidepressants to decrease one or both of these symptoms. In terms of pain, future studies are

warranted that evaluate the direct relationship between dyspnea and pain in patients with cancer. These further studies will pave the way to design more precise targeted interventions and improve their efficacy for oncology patients with dyspnea and pain. Lastly, studies are needed that test the psychometric properties of new assessment tools that evaluate a variety of respiratory symptoms (e.g., shortness of breath, difficulty breathing, chest tightness, cough) as a “bundle”.

The identification of molecular markers for dyspnea is still in its infancy. Our study is the first to suggest that a number of inflammatory pathways and their interactions contribute to the development of dyspnea in cancer patients. In addition, preliminary evidence suggests that some of these inflammatory mechanisms that underlie dyspnea in oncology patients are reported in other respiratory diseases. Future studies need to identify distinct shortness of breath profiles in patients with common respiratory conditions and evaluate for perturbations in inflammatory pathways. In addition, longitudinal studies are needed to assess for associations between changes in shortness of breath and changes in gene expression and pathway perturbations. Finally, the use of samples from the respiratory tract (e.g., sputum) may allow for the identification of local effects of inflammatory mechanisms in the development of dyspnea in patients with cancer.

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