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Psychological correlates of sleep quality in lung cancer patients under chemotherapy: A single-center cross-sectional study

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Abstract

Objectives: Disturbed sleep is a common complaint of lung cancer patients undergoing active oncologic treatment. We aimed to clarify the extent to which psychological symptoms, coping strategies, and social support interfere with sleep quality and whether they mediate the relationship between sleep quality and fatigue or functional capacity in a sample of chemotherapy treated lung cancer patients.

Methods: Lung cancer patients attending an oncology unit for scheduled chemotherapy cycles completed questionnaires assessing their sleep quality, fatigue, depression, anxiety, stress, coping, social support, symptoms of pain, dyspnea, and cough, and sleep hygiene practices. Demographic and disease-related characteristics were obtained from patients' medical records and treating physicians rated their functional status. Multivariate regression and mediation analyses were applied to test the study's hypotheses.

Results: One hundred nineteen patients were enrolled, 58.2% of whom were identified as poor sleepers. After adjusting for age, gender, comorbidities, concomitant medications, cancer stage, prior and ongoing treatment, sleep hygiene, and symptoms, there was a statistically significant association between poor sleep quality and anxiety (odd`s ratio [OR] 1.17 [95% CI, 1.01-1.35]), stress (OR 1.14 [95% CI, 1.04-1.25]), and positive coping (OR 1.15 [95% CI, 1.02-1.31]). Poor sleep quality was an independent correlate of fatigue (*B* 1.56 [95% CI, 0.61-2.50]) and low performance status (OR 5.17 [95% CI, 1.60-16.72]); stress symptoms partially mediated the relationship between sleep quality and fatigue ($P = .030$).

Conclusions: Higher psychological burden predict sleep disturbances and contribute to increased fatigue in lung cancer patients undergoing chemotherapy. Effective psychoeducational interventions may benefit these populations.

KEYWORDS

adaptation, psychological, anxiety, cancer, depression, fatigue, oncology, physical functional performance, sleep, social support, stress, psychological

1 | INTRODUCTION

1.1 | Background

Cancer patients suffer from higher rates of sleep disturbances than both the general and the psychiatric population.[1] Insomnia symptoms, excessive daytime sleepiness, and restless legs were found to be the most prevalent complaints,[2] while they present with reduced sleep duration and efficiency, increased daytime napping, and difficulty in maintaining both sleep and wakefulness.[3] Their etiology is most likely multifactorial, with disease- and treatment-related factors interacting with various demographic, lifestyle, and psychological factors and resulting in altered sleep regulation processes, blunted circadian rhythms, and maladaptive behaviors perpetuating the problem.[4]

Lung cancer patients are a unique cancer population, often having advanced stage disease and high symptom and comorbidity burden. In previous studies,[5-8] prevalence of poor sleep quality was consistently over 50% of participants, underlining the challenge faced by the health care practitioners in diagnosis, severity assessment, and treatment of these disorders in this highly at-risk population. Independent associations with fatigue[9] and poor functional status[6] have also been identified.

Psychological factors, especially anxiety and depression, have emerged as important contributors of poor sleep quality in cancer patients, both in treatment[10-12] and palliative[13,14] settings. Few studies[7,9,15] have explored the same association exclusively in lung cancer patients, yielding mostly inconsistent results, the main reason being not considering the confounding effects of environmental and disease-related factors that influence sleep quality in those populations.

1.2 | Objectives

The study's primary objective was to identify the psychological factors that independently influence the sleep quality of lung cancer patients undergoing active chemotherapy treatment, with focus on symptoms of depression, anxiety, and stress, coping styles, and perceived social support. Secondary, we aimed to determine whether the same psychological factors mediate the relationship between sleep quality and fatigue or performance status.

2 | METHODS

2.1 | Study design

We employed a cross-sectional survey design using validated questionnaires in a sample of lung cancer patients undergoing chemotherapy in a university oncology unit in Greece. The study was approved by the Institutional Review Board of the "Sotiria" Regional Chest Diseases Hospital of Athens (protocol number 22921/29-11-2017).

2.2 | Setting

Lung cancer patients were attending the Oncology Unit of the 3rd Department of Medicine, Athens Medical School for their scheduled chemotherapy cycles. Recruitment occurred in two waves from November 2017 to April 2018. After explaining the study's purpose and determining eligibility for inclusion, written informed consent was obtained and a set of questionnaires was administered. Participants were instructed to fill them on that same day, and completed sets were gathered either at the end of patient's stay or during their next appointment. Information was also collected from patients' medical records and treating physicians.

2.3 | Participants

We recruited a convenience sample of participants by asking all patients that presented for treatment on enrollment days to take part. They were eligible for inclusion if they were over 18 years old with a histologically or cytologically proven diagnosis of lung cancer and had received at least one chemotherapy cycle (conventional or immunotherapy) over the previous trimester. They were excluded if they were diagnosed with a specific sleep disorder (except from insomnia) or a major psychotic disorder, had severe cognitive impairment, or were unable to read or understand the protocol and study instruments.

2.4 | Variables

Subjective sleep quality was the study's primary outcome. Cancer-related fatigue (CRF) and functional status were secondary outcomes. Psychological factors that were considered as predictors were symptoms of depression, anxiety, and stress, coping methods, and social support. Variables treated as confounders were sleep hygiene factors and current symptoms of pain, dyspnea, and cough. Age, gender, comorbidities, concomitant medications, cancer stage, occurrence of brain metastases, history of surgery or radiation therapy on previous trimester, and type of chemotherapy were considered potential effect modifiers.

2.5 | Data measurement

2.5.1 | Sleep quality

Greek version of the Pittsburgh Sleep Quality Index (GR-PSQI) was used to quantify the sleep quality of participants. It consists of 19 individual items that enquire about sleep disturbances during the last month and form seven subscales, the sum of which generate a global score. A cut-off global score greater than 5 has been traditionally used to distinguish poor from good sleepers.[16] Psychometric properties of the GR-PSQI have been tested in cancer patients.[17] In our sample, internal consistency for the seven components was acceptable (Cronbach α = .76).

2.5.2 | Fatigue

Greek version of the Brief Fatigue Inventory (BFI-Gr) was used to assess the severity and impact of CRF on study participants. It includes three items on fatigue severity and six on fatigue interference with daily functioning during previous 24 hours, which are scored in an 11-point scale. All items are then averaged to produce a global CRF score, with lower scores corresponding to less fatigue.[18] Its psychometric properties were found to be satisfactory in Greek cancer patients.[19] Excellent internal consistency (Cronbach α = .98) was obtained in our sample.

2.5.3 | Functional status

Treating physician judged the functional capacity of participants on the same chemotherapy day according to the Eastern Cooperative Oncology Group Performance Status Scale (ECOG PS). The scale measures patients' level of functioning in terms of their ability to care for themselves, daily activity, and physical ability.[20] There are five grades ranging from fully active to completely disabled. Assessment was part of the daily routine of the unit and not particularly performed for the purpose of this study; in that way, assessing physicians were not aware of the patient's participation in the study.

2.5.4 | Psychological factors

Psychological symptoms were measured with the short version of the Depression Anxiety Stress Scales (DASS-21) in its Greek translation.[21] They constitute a set of three scales, each containing seven items, where responders rate their negative emotional state over the past week in a 4-point scale. Item scores are then summed and doubled to obtain an overall score for each dimension, with lower scores representing healthier state.[22] Depression and Anxiety scales of the original version have been recently validated in oncologic patients.[23] The instrument exhibited good reliability measurements in the current sample (Cronbach αs = .90, .81, and.88, respectively).

Coping styles were assessed with the Greek version of the Brief COPE.[24] It has 14 subscales of two items each and measures ways of dealing with stress in a 4-point scale, with higher scores meaning greater coping strategies.[25] Psychometric properties of seven subscales of the original Brief COPE were evaluated in patients with advanced lung cancer and they exhibited good construct validity.[26] Internal consistency of all items in the present study was good (Cronbach α = .84).

The Medical Outcomes Study Social Support Survey-Greek version (MOS-SSS-G) was used to measure perceived social support. It contains 19 items with 5-point scale responses that are averaged to produce an overall index. Higher scores represent greater social support.[27] The MOS-SSS-G has been validated in a sample of caregivers of children with cancer.[28] Excellent reliability was evident in our sample (Cronbach α = .96).

2.5.5 | Sleep hygiene factors

A 14-item questionnaire, designed by the researchers, was administered to evaluate sleep hygiene factors, such as sleep/wake schedules, use of caffeine, alcohol, or tobacco prior to bedtime, presleep activities or worries, and sleeping environment during the past month. Responses were available in a 4-point Likert scale, and the scores were averaged to provide a single sleep hygiene measure, with lower score reflecting healthier sleep habits. Its internal consistency was borderline acceptable (Cronbach α = .64).

2.5.6 | Symptoms

The Greek Brief Pain Inventory (G-BPI) was utilized to assess the severity and impact of pain on the last 24 hours. It constitutes of four and seven items that are scored on an 11-point scale and then averaged to produce a pain severity and a pain interference measure, respectively. Lower scores denote lower severity and less impact on daily functioning.[29] The translated version showed acceptable psychometric properties in cancer patients.[30] Excellent internal consistency was found in the present sample (Cronbach α = .94 for severity and.96 for interference scale).

Participants were also provided a 100-mm visual analogue scale to rate the severity of dyspnea and cough over the past 24 hours. Previous research has confirmed the validity of self-assessment of cancer-related symptoms with linear analogue scales.[31]

2.5.7 | Demographic, disease-, and treatment-related factors

These variables were determined after review of the patient's medical record. We used the Charlson Comorbidity Index to quantify the comorbidity burden of participants. It is a weighted index that measures both the amount and the severity of comorbid diseases and was originally validated in a cohort of breast cancer patients.[32] We recorded concomitant medications of the following categories for their capacity to influence sleep: antidepressants, antipsychotics, anxiolytics, antiepileptics, and opioids. Type of chemotherapy was classified as initial cytotoxic, maintenance cytotoxic, or immunotherapy.

2.6 | Bias

For the assessment of possible response bias, demographic and disease-related characteristics that could modify the observed associations were compared between respondents and nonrespondents.

2.7 | Study size

Hypothesizing a 50% prevalence of poor sleep quality in subjects scoring around the mean in each DASS-21 scale and a 15% increase in prevalence for each score elevation by one standard deviation (SD) and assuming a 15% squared multiple correlation with other

confounding variables, we determined the need for a sample size of 116 participants to reach 80% statistical power in the 5% significance level in order to examine if the odds of poor sleep quality are predicted by psychological symptoms in logistic regression analysis.

2.8 | Quantitative variables

For sleep quality, a cut-off global PSQI score greater than 5 discriminated poor from good sleepers. For functional status, participants were divided in three categories according to ECOG PS grading (PS = 0, PS = 1, and PS $\geq$ 2). Cancer stage was dichotomized in metastatic and nonmetastatic. Pain was entered as a single variable in multivariate analyses, averaging the pain severity and pain interference scales of the G-BPI.

In order to identify broader dimensions of coping styles, we employed a principal components exploratory factor analysis with varimax rotation on the 14 subscales of the Brief COPE. Three components were extracted, named as positive coping (including active coping, positive reframing, planning, humor, and acceptance), negative coping (including denial, substance use, behavioral disengagement, venting, and self-blame), and comfort/support seeking coping (including self-distraction, emotional support, instrumental support, and religion). As a result, we created three summary scales by adding the scores of the included subscales (Cronbach αs = .78, .68, and.80) and used them in subsequent multivariable analyses.

2.9 | Statistical methods

In descriptive statistical analysis, categorical variables were expressed in the form of frequency count (%) and continuous variables as mean (SD) or median (interquartile range). Correlations between predictors and outcomes were tested using the Spearman rank-order correlation coefficient. Good and poor sleepers were compared using the chi-square test for categorical and Student's *t* test or Mann-Whitney *U* test for continuous variables.

To examine the independent impact of predictors on primary and secondary outcomes, we ran a series of regression analyses controlling for confounders and effect modifiers. For primary outcome, we separately handled each psychological factor as predictor in binary logistic regression analyses. Sleep quality was then tested as predictor of CRF and functional capacity in linear and ordinal regression analyses, respectively, while each psychological factor was evaluated for significant mediation effect in the above relationships using the Sobel test.[33] Subgroup differences were examined with two-way interactions entered as final step in regression models.

Missing data were addressed in multivariate analyses with multiple imputation under the missing at random assumption. Fifty sets of data were created, and the regression analyses results were pooled in single estimates. The estimates were thereafter compared with those obtained from analyses on cases with complete data.

All analyses were conducted with the statistical software package SPSS 25.0, and statistical significance was considered at the 5% level.

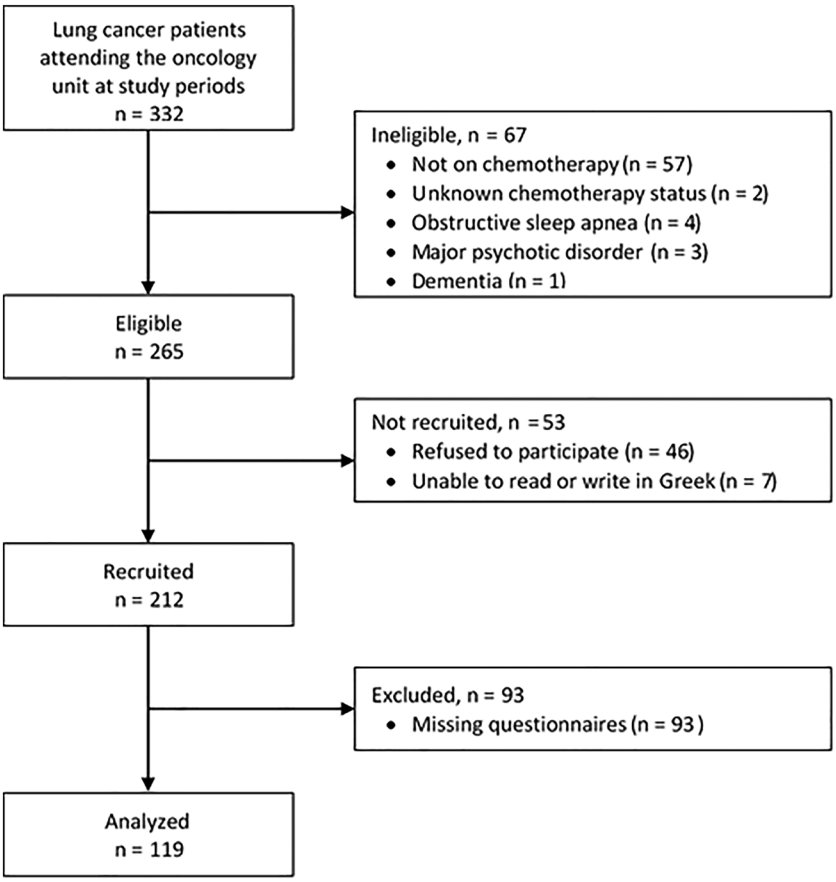

FIGURE 1 Study flow diagram

3 | RESULTS

3.1 | Participants

Of the 332 lung cancer patients sampled during enrolment period, we excluded 67 individuals for not fulfilling the eligibility criteria. Of the 265 eligible patients, 46 refused to participate and seven were unable to read or write in Greek, while another 93 patients did not return the questionnaires, yielding a final sample of 119 participants and an overall response rate of 44.9% of eligible subjects (Figure 1).

3.2 | Descriptive data

Most participants were men (71.4%), had metastatic lung cancer (77.3%), and were receiving initial cytotoxic chemotherapy (61.3%). Their mean age was 64 years and had an average of one comorbidity. There were not significant differences in demographics and disease- or treatment-related factors between respondents and nonrespondents, except from age (Table S1). Respondents were younger by 4 years on average than nonrespondents, a difference that was statistically significant ($P < .001$).

Summary measures of predictors, confounders, and outcomes are presented in Table S2, along with missing data frequencies and Spearman rank order correlations; 58.2% of the participants with nonmissing PSQI data were classified as poor sleepers. Compared with good sleepers, they were prescribed opioids more often, exercised worst sleep hygiene practices, complained more about pain, dyspnea, and fatigue, had higher psychological burden, and were less functional (Table S3).

3.3 | Main results

In Table 1, we report the pooled odds ratios (ORs) and the corresponding 95% CIs of being poor sleeper for every one-unit increase in the relevant scores of the psychological scales, after multiple imputation of missing data. We tested five models with gradually increasing covariate adjustment: the first was unadjusted; the second adjusted for demographics, comorbidities, and concomitant medications; the third further adjusted for disease- and treatment-related factors; the fourth added sleep hygiene factors; and the fifth included all previous variables plus symptoms of pain, dyspnea, and cough.

In the fully adjusted model, every one-unit increase in the score of the DASS-21 Anxiety and Stress scale was associated with a 17% (OR 1.17 [95% CI, 1.01-1.35]) and a 14% (OR 1.14 [95% CI, 1.04-1.25]) increase, respectively, in the odds of being poor sleeper. The odds for the score on the DASS-21 Depression scale were attenuated and became nonsignificant after adjustment for symptoms (fully adjusted OR 1.06 [95% CI, 0.99-1.14]), whereas the odds for the positive coping factor were magnified and became significant after the inclusion of disease-related factors in the model (fully adjusted OR 1.15 [95% CI, 1.02-1.31]).

To test the effect of poor sleep quality on the secondary outcomes, we fitted linear regression models for fatigue and ordinal regression models for functional status (Table 2), controlling for different levels of confounders. In complete models, poor sleepers had significantly higher fatigue scores by 1.5 point (*B* 1.56 [95% CI, 0.61-2.50]) and were five times more likely to have worst ECOG PS rating (OR 5.17 [95% CI, 1.60-16.72]) than good sleepers. When psychological factors were examined as mediators of the above associations,

TABLE 2 Influence of poor sleep quality on fatigue and functional status in linear and ordinal regression models with increasing covariate adjustment

	Fatigue		Performance Status	
	B	95% CI	OR	95% CI
Model 1	2.70	1.68-3.72	6.24	2.40-16.20
Model 2	2.42	1.36-3.49	6.25	2.21-17.70
Model 3	2.50	1.39-3.61	4.68	1.58-13.86
Model 4	1.56	0.61-2.50	5.17	1.60-16.72

Note. Model 1: unadjusted. Model 2: adjusted for gender, age, Charlson Comorbidity Index, and use of concomitant medications. Model 3: adjusted for cancer stage, history of brain metastases, recent surgery or radiation therapy, chemotherapy type, and model 2 variables. Model 4: adjusted for pain, dyspnea, cough, and model 3 variables.

Abbreviations: *B*, beta coefficient; CI, confidence interval; OR, odds ratio.

TABLE 1 Influence of psychological factors on poor sleep quality in binary logistic regression models with increasing covariate adjustment

	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)	Model 5 OR (95% CI)
Depression	1.09 (1.03-1.15)	1.09 (1.03-1.16)	1.11 (1.04-1.19)	1.09 (1.02-1.17)	1.06 (0.99-1.14)
Anxiety	1.17 (1.07-1.29)	1.19 (1.07-1.33)	1.22 (1.08-1.38)	1.19 (1.05-1.35)	1.17 (1.01-1.35)
Stress	1.12 (1.05-1.20)	1.15 (1.07-1.24)	1.17 (1.08-1.28)	1.16 (1.06-1.26)	1.14 (1.04-1.25)
Positive coping	1.06 (0.99-1.13)	1.09 (1.00-1.19)	1.13 (1.01-1.25)	1.13 (1.01-1.27)	1.15 (1.02-1.31)
Negative coping	1.08 (0.99-1.18)	1.07 (0.98-1.18)	1.11 (0.99-1.23)	1.05 (0.93-1.18)	1.04 (0.91-1.18)
Comfort/support seeking coping	1.04 (0.97-1.12)	1.05 (0.96-1.14)	1.05 (0.95-1.15)	1.04 (0.94-1.15)	1.04 (0.92-1.16)
Social support	0.99 (0.98-1.01)	0.99 (0.98-1.01)	0.99 (0.97-1.00)	0.99 (0.97-1.01)	1.00 (0.98-1.02)

Note. Model 1: unadjusted. Model 2: adjusted for gender, age, Charlson Comorbidity Index, and use of concomitant medications. Model 3: adjusted for cancer stage, history of brain metastases, recent surgery or radiation therapy, chemotherapy type, and model 2 variables. Model 4: adjusted for sleep hygiene practices and model 3 variables. Model 5: adjusted for pain, dyspnea, cough, and model 4 variables.

Abbreviations: CI, confidence interval; OR, odds ratio.

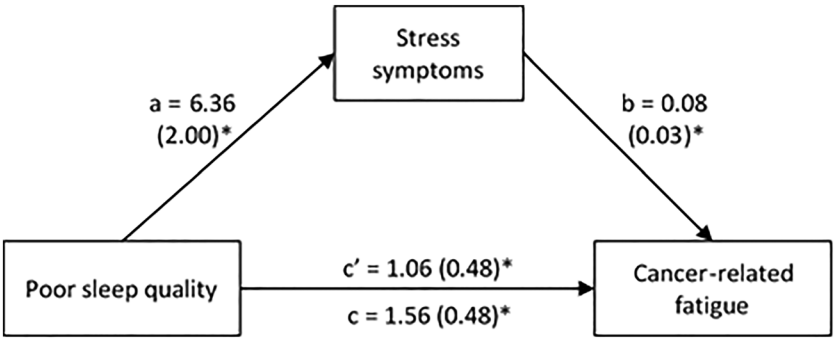

FIGURE 2 Path diagram for the mediation effect of stress symptoms on the association between sleep quality and fatigue in chemotherapy treated lung cancer patients (Sobel test 2.17 [SE 0.23], $P = .030$). *$p < 0.05$

there was a significant indirect effect of poor sleep quality on CRF via stress symptoms (Sobel test 2.17 [SE 0.23], $P = .030$) (Figure 2).

3.4 | Other analyses

To account for possible response bias, we performed subgroup analysis by gender and age. In all the above fully adjusted regression analyses, we entered interaction terms between predictors and gender or age and tested their significance. However, none of the two-way interactions examined reached statistical significance (*P*s > .05, data not shown).

We also repeated the multivariate analyses with listwise deletion of missing data. We obtained robust estimates, like those already reported, for both the primary and the secondary outcome, including the mediation analysis.

4 | CONCLUSIONS

4.1 | Summary of findings

The key result of our study is the association of anxiety and stress symptoms and positive coping practices with poor sleep quality in lung cancer patients on chemotherapy, independently of demographics, sleep hygiene factors, and disease- and treatment-related characteristics. Furthermore, perceived stress symptoms partially mediate the relationship between poor sleep quality and CRF.

4.2 | Study limitations

Our study suffers from several limitations. The cross-sectional design employed is unable to identify causal pathways between the variables. We used a convenience sample from a single center, which might limit the generalizability of the findings. Younger and female patients were more likely to respond to the survey, which is considered a source of bias, since they may have a higher burden of sleep disturbances. Furthermore, the overall response rate was low, and a possibility exists for good sleepers to avoid being surveyed, as they might not be motivated by the study's purpose. One minor drawback could also be the different settings that patients were allowed to complete the questionnaire. There is a possibility for participants responding in a different manner in their home environment compared with the hospital, mostly in terms of available time. Finally, sleep quality was assessed subjectively; a degree of overestimation or underestimation by the patients could not be ruled out.

4.3 | Interpretation

Most chemotherapy-treated lung cancer patients exhibited poor sleep quality, finding consistent with previous research.[5-8] Moreover, disease- and treatment-related factors, such as cancer stage, previous and current therapies, had no significant impact on sleep, unlike symptoms and functional or psychological status.

We observed independent associations between poor sleep quality and anxiety and stress symptoms of lung cancer patients. However, the influence of depressive symptoms was attenuated by the confounding effect of other physical symptoms, highlighting the detrimental effect of symptom burden on the patient's emotional state. The hypothalamic-pituitary-adrenal axis activation because of increased physical and psychological stress was found to have the most pronounced effect on sleep quality of newly diagnosed lung cancer patients in a recent study,[9] supporting our conclusions.

The finding that positive coping strategies were related to poorer sleep quality is indeed unexpected and contrary to previous research.[34] We hypothesize that positive coping may be a consequence of poor sleep rather than a precursor and that good sleepers have generally low stress levels and do not necessary need coping skills.

Sleep disturbances were also independently associated with poorer functional status and higher fatigue levels, while stress symptoms were identified as a significant mediator of the latter. The same relationships among sleep, fatigue, and psychological burden have been identified in patients with hepatocellular carcinoma.[35]

A putative mechanism behind the observed associations could be the production of inflammatory cytokines as response to the tumor itself or the applied treatments. The cytokine-induced sickness behavior has been proposed as a shared underlying feature of multiple symptom clusters in cancer patients and certain neuro-immunologic interactions may well be the common denominator explaining both mood disorders and sleep/wake disruption.[36] This theory may also account for the bidirectional relationships that are generally expected

between sleep disturbance and other physical or psychological symptoms. In a recent study, poorer sleep quality was related to increased levels of inflammatory biomarkers in lung cancer patients undergoing chemotherapy.[37] Future research should concentrate more on clarifying these complex processes.

4.4 | Generalizability

Our study involved lung cancer patients with a distinct profile, that is, advanced stage, mostly ambulatory with retained functionality, and on active oncologic treatment with frequent visits to the oncology unit. Early-stage patients, those receiving oral anticancer agents, and cancer survivors may have less disease or treatment burden and less disruption of their daily routines and thereafter present with different sleep patterns. The same could be true for patients in palliative and hospice settings, since they often experience overwhelming symptoms and have largely diminished functional status. As a result, it is possible that our findings cannot be generalized to the whole lung cancer population. However, this group of patients is more likely to seek help from oncologists for their sleep problems and that is why this study focused on them.

4.5 | Clinical implications

Oncologists and nurses who care for lung cancer patients under chemotherapy should be aware of the impact that anxiety and stress symptoms have on sleep quality and fatigue, independent of disease factors, sleep habits, and symptoms. Consequently, symptom management and sleep hygiene education, although still important, may not be sufficient to fully alleviate sleep disturbances in this population. In this context, consultation with psychologists and other mental health professionals should be offered to all patients with insomnia and poor sleep, while psychoeducational interventions implemented throughout the duration of treatment might be effective in reducing the psychological burden and enhancing sleep quality. In a recent meta-analysis of unselected lung cancer patients,[38] psychoeducational interventions showed significant short-term effects on sleep quality, providing further evidence for the role of psychological factors in patients' sleep.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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