

## SHORT REPORT

## Oncology

# Insomnia in patients with advanced lung cancer admitted to palliative care services

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## Abstract

**Aim:** To assess the prevalence of insomnia and possible associated factors in patients with advanced lung cancer admitted to different settings of palliative care.

**Methods:** Secondary analysis of a consecutive sample of patients with advanced lung cancer receiving palliative care. Epidemiological and clinical data, treatments received in the last month, Karnofsky status, Edmonton Symptom Assessment System (ESAS), Athens Insomnia Scale and the Hospital Anxiety and Depression Scale (HADS), as well as concomitant medical treatment were recorded.

**Results:** One-hundred-eight-two patients with advanced lung cancer were surveyed. The mean age was 69.9 years (SD 10.8), and 121 patients (66%) were men. The majority of patients showed consistent levels of insomnia. A poor Karnofsky level, pain, nausea, and drowsiness, time from diagnosis (1-3 years), HADS anxiety, and HADS depression, were positively associated with insomnia.

**Conclusions:** About 50% of patients with advanced lung cancer admitted to palliative care services had relevant insomnia. Several factors associated with insomnia have been identified and should prompt physicians for a careful examination and subsequent treatment.

## 1 | INTRODUCTION

Lung cancer is the most important cause of death associated with cancer. Despite the improvement in diagnosis and treatment, this population has a poor prognosis.

Patients with lung cancer experience a significant symptom burden along the course of disease trajectory, particularly in the advanced stage.<sup>1</sup> A poor symptom control could negatively affect treatment adherence and therapeutic outcomes.<sup>2,3</sup>

Insomnia has been reported to be more frequent in cancer patients than in general population, with a variable prevalence ranging from 24% to 95%,<sup>3-6</sup> suggesting that sleep disturbances develop in a substantial proportion of cancer patients. Of interest, sleep quality was found to be highly correlated with survival.<sup>7</sup>

Although insomnia is common and may have a negative impact on quality of life, it has received little attention, differently from

other symptoms cancer-related.<sup>8</sup> As few papers have assessed this subject, more information is needed to characterise insomnia in patients with advanced lung cancer.

The aim of this study was to assess the prevalence of insomnia and the possible factors associated with insomnia in patients with advanced lung cancer admitted to palliative care services.

## 2 | METHODS

This is a secondary analysis of a study assessing insomnia in patients with advanced cancer in different palliative care settings. This large multicenter study was performed for a period of 6 months from January to June 2015 in six centers in Italy. Informed consent and ethical committee approval were obtained. Inclusion criteria were: A diagnosis of lung cancer, and ability to provide the information requested.

## 2.1 | Patients

In the original study inclusion criteria were a diagnosis of cancer, informed consent, and ability to provide the information requested. Exclusion criteria were cognitive problems at time of the interview. Comatose patients, severely ill patients or with an immediate poor prognosis were also excluded, to avoid unnecessary psychological burden.

From the original sample of 820 patients with advanced cancer, those with a diagnosis of lung cancer were selected for a further subanalysis.<sup>9</sup>

## 2.2 | Data collection

Epidemiological and clinical data, Karnofsky level, and education levels were recorded, as well as the Edmonton Symptom Assessment System (ESAS). ESAS is validated system to assess the principal psychological and physical symptoms in advanced cancer patients. Each symptom is scored in a numerical scale from 0 to 10. Treatments received in the last month and concomitant medical treatment were collected, as well as the use of analgesics or adjuvant drugs.

At admission, patients were administered the Athens Insomnia Scale (AIS). AIS consists of eight items. Five items assess difficulties with sleep induction, awakening during the night, early morning awakening, total sleep time, and sleep quality. Other three items assess the next-day consequences of insomnia, including sense of well-being, overall quality of sleep, and sleepiness during the day. Each item of the AIS is rated on a scale from 0 (no problem at all) to 3 (very serious problem). The sum of these eight items ranges from 0 to 24. A score of  $\geq 6$  corresponds to a sleep disturbance.<sup>10</sup>

The Hospital Anxiety and Depression Scale (HADS) was recorded. This tool consists of 14 items distributed in two subscales, to assess anxiety (seven items, HADS-A) and depression (seven items, HADS-D). Each item of the HADS is rated 0 to 3, so that the total score ranges from 0 to 42. A score  $\geq 11$  is considered to be the cut-off for psychological distress.<sup>11-13</sup>

AIS was used for determining the level of sleep disturbances or insomnia. Patients' characteristics, ESAS and HADS were studied as possible associated variables.

## 2.3 | Statistical analysis

The study aims at describing the sleep disturbances in patients with advanced lung cancer. Descriptive statistics have been provided according to clinical symptoms, patients' characteristics, socio-economic and educational conditions and treatment. Statistical association patterns have been tested where feasible with  $\chi^2$  test and  $\chi^2$  trend test setting I type error at 5%. Regression models have been carried out assuming as continuous response the AIS score. The regression models were performed using symptoms, socio-economic

### What's known

- A few studies reported that patients with lung cancer may develop insomnia along the course of disease.
- In small studies a correlation with depression, anxiety, fatigue, quality of life, and pain scores was found.

### What's new

- In this large cross-sectional study of advanced cancer patients, about 50% of patients had intense-maximum sleep disturbances, assessed by a validated tool for insomnia.
- Patients with higher levels of pain, drowsiness, depression, anxiety, and longer time from diagnosis were more likely experience severe sleep disturbances.

and educational variables, disease oriented treatment, drugs administered and HADS score. These models were used in order to choose statistically significant explanatory variables used to model and adjust the AIS outcome. The statistical analysis has been performed using the statistical software STATA version 14.

## 3 | RESULTS

From 820 advanced cancer patients recruited in the original study, 182 patients with lung cancer were selected for this secondary analysis.

### 3.1 | Patients' characteristics

The mean age was 69.9 years (SD 10.8), and 121 patients (66.4%) were men. Recent treatments were chemotherapy (n = 46, 25.4%), radiotherapy (n = 9, 5.0%), palliative care (n = 116, 64.1%), others (n = 10, 5.5%). Other demographic characteristics are presented in Table 1. Current drugs medications included (rank order): corticosteroids (130 patients, 71.4%), opioids (125 patients, 68.7%), benzodiazepines (46 patients, 25.3%), antidepressants (19 patients, 10.4%), neuroleptics (19 patients, 10.4%; Table 1).

### 3.2 | Insomnia and associated factors

The majority of patients showed consistent sleep disturbances (AIS  $\geq 6$ ) with 48.5% of patients having intense-maximum sleep disturbances (Table 2).

The correlations between AIS scores and variables taken into consideration, adjusted by age and gender, are presented in table 3 and 4.

**TABLE 1** Characteristics of patients with advanced lung cancer

Number of patients	182
Age (years) mean (SD)	69.9 (10.8)
Gender (men/women)	121 (66.5%)/61 (33.5%)
Karnofsky mean (SD)	45.9 (14.9)
Anticancer treatment	
Chemotherapy	46 (25.1%)
Radiotherapy	9 (5.0%)
Palliative care	116 (64.1%)
Others	10 (5.5%)
Marital status	
Single	10 (5.7%)
Widowed	36 (20.7%)
Divorced/separated	2 (1.1%)
Married/cohabiting	126 (72.4%)
Education	
Primary	37 (20.8%)
Secondary	83 (46.6%)
Tertiary or undergraduate	46 (25.8%)
Degree	12 (6.7%)
Drugs	
Opioids	125 (68.7%)
Corticosteroids	130 (71.4%)
Benzodiazepines	46 (25.3%)
Antidepressants	19 (10.4%)
Neuroleptics	19 (10.4%)
Psychostimulants	2 (1.1%)

**TABLE 2** Number of patients with the different ranges of AIS values

No sleep disturbances	16.8%
Mild sleep disturbances	16.1%
Moderate sleep disturbances	18.6%
Intense sleep disturbances	23%
Maximum sleep disturbances	25.5%

Insomnia was associated with a poor Karnofsky level ( $P = .009$ ), with pain ( $P = .004$ ), nausea ( $P = .007$ ), and drowsiness ( $P = .004$ ), and with time from diagnosis (1-3 years;  $P = .014$ ; Table 4).

The use of opioid analgesics or adjuvant drugs was not associated with sleep disturbances. Indeed, insomnia was associated with the use of non-opioid analgesics ( $P = .019$ ). Seventy-eight patients (46.7%) had anxiety (HADS-A  $\geq 11$ ), and 102 patients (62.6%) had depression (HADS-D  $\geq 11$ ). There was a positive correlation between HADS-A and HADS-D with insomnia. In the multivariate analysis pain, drowsiness, HADS-A, HADS-D, and time from diagnosis were independently associated with AIS score (Table 4).

## 4 | DISCUSSION

In this secondary analysis of a cross-sectional study about 50% of patients with advanced lung cancer had intense-maximum sleep disturbances. Pain, drowsiness, HADS-A, HADS-D and time from diagnosis were found to be independently associated with AIS score.

Most data regarding sleep disorders are gathered from patients who were diagnosed lung cancer, were undergoing chemotherapy, or were long-survivors.<sup>14-17</sup> Studies have reported a high psychological burden affecting quality of life.<sup>18</sup> Of interest, sleep quality was found to be prognostic factor for survival.<sup>7</sup>

Retrospective analyses of advanced cancer outpatients showed that sleep problems were associated with the use of sedatives, pain, fatigue, and poor well-being.<sup>19,20</sup> In patients admitted to an acute palliative care unit, anxiety was associated with more difficulties in falling asleep, produced a less restoring sleep and nightmares, while depression was associated with early awaking, nonrestorative sleep, fatigue, and nightmares.<sup>21</sup> In a large prospective study consistent sleep disturbances (moderate to maximum) were found in about 60% of patients. Aged patients were less likely to have sleep disturbances, whereas a poor Karnofsky level was significantly associated with sleep problems. Hormone therapy and the use of opioids and corticosteroids were positively associated with sleep disturbances. Moreover, there was a positive correlation of HADS-A and HADS-D scores with insomnia.<sup>9</sup>

Data regarding patients with advanced lung cancer are limited. In a small Japanese study more than half of the patients with lung cancer had sleep disturbances. A correlation between AIS, HADS, fatigue, quality of life, and pain scores was found.<sup>22</sup> Sleep disturbances affected 62.5% of inpatients with advanced lung cancer. These patients were more likely to have severe respiratory symptoms and a lower quality of life.<sup>8</sup> In a large prospective multicenter study, about 50% of patients with lung cancer reported difficulty initiating or maintaining sleep, and 60.8% reported daytime sleepiness. The prevalence of insomnia was 44.7%. Patients with moderate to severe severity pain, dyspnea, and anxiety were independently related to insomnia.<sup>23</sup>

Taken together, this information is consistent with data of the present study. Relevant sleep disorders are frequently observed in patients with advanced lung cancer and are likely to be associated with psychological factors and diurnal drowsiness, possibly as a consequence of a less restoring sleep and pain that commonly impede a restoring sleep.

Of interest, patients with advanced lung cancer may also have other chronic lung diseases that can impact lung function and may reduce sleep quality. Moreover, there is a relationship between lung cancer and sleep related to other conditions such as disruption of circadian rhythm and obstructive sleep apnoea. Fragmented sleep and intermittent hypoxia may also initiate malignant transformation and promote changes in the tumour microenvironment, and disrupt immunosurveillance. Thus, this condition may hasten tumour proliferation and increase local and metastatic invasion. It is now understood

	AIS	$\hat{\beta}_i$	SD	P	[95% CI]	
Adjustment Covariates	Age	0.02	0.04	.607	-0.07	0.11
	Gender	-0.02	0.91	.991	-1.82	1.80
	Karnofsky	0.01	0.03	.973	-0.06	0.06
HADS scale	HADS anxiety	2.17	0.58	.000	1.03	3.31
	HADS depression	2.75	0.63	.000	1.49	3.99

**TABLE 3** AIS vs. HADS anxiety and depression adjusted by age and gender

AIS score	$\hat{\beta}_i$	$\widehat{SD}_i$	P	[95% CI]	
Age	0.03	0.04	.496	-0.05	0.11
Gender	1.03	0.89	.251	-0.74	2.80
Karnofsky	0.02	0.03	.523	-0.04	0.08
Pain	0.34	0.16	.033	0.03	0.65
Nausea	-0.36	0.19	.062	-0.73	0.02
Drowsiness	0.58	0.16	.000	0.27	0.89
HADS anxiety	1.98	0.54	.000	0.91	3.05
HADS depression	2.21	0.60	.000	1.01	3.40
Analgesics non opioids	0.22	0.93	.816	-1.63	2.06
Time from diagnosis (1-3 years)	-2.03	0.93	.031	-3.89	-0.19

**TABLE 4** Overall regression model adjusted by the preceding statistically significant covariates

that sleep deprivation, fragmentation and hypoxia negatively predict survival shining light on the role of sleep on the innate and adaptive immune systems.<sup>24-26</sup>

The study has some limitations due to the nature of a cross-sectional design. It is recommended that the mediating effect of insomnia on the relationship with the examined variables be further examined in longitudinal studies. Secondly, data were gathered from a secondary analysis of a large study performed in different settings of palliative care. However, the aim was exactly to assess the risk of insomnia in a sufficient sample of patients with advanced lung cancer, when they were admitted to palliative care services. Finally, the use of substances potentially having an impact on sleep quality, for example caffeine, was not assessed.

## 5 | CONCLUSION

As restorative sleep is fundamental in such a fragile population, physicians should be aware about this problem, identifying the most frequent risk factors of insomnia. In particular, the psychological profile should be assessed, and pain properly treated. Further longitudinal studies should provide information about the changes of sleep disturbances along the course of disease and how the prevention or the treatment of some factors may be of benefit for patients with advanced lung cancer.

## CONFLICT OF INTEREST

No conflict of interest to be declared by all the authors.

## ETHICAL APPROVAL

The research involved humans. All procedures performed in were in accordance with ethical standards of the institutional and/or nationale research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants.

## DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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