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Pain, anxiety and depression are predictive of poor sleep quality in patients with head and neck squamous cell carcinoma

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Tese apresentada à Faculdade de Odontologia de Araçatuba da Universidade Estadual Paulista (Unesp), para obtenção *do título de ''Doutora em Odontologia''*- Área de Concentração: Estomatologia e Psiconeuroimunologia.

Orientador: Prof. Assoc. Dr. Daniel Galera Bernabé.

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Epígrafe

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Elisabeth Kübler-Ross

Resumo

Valente GMK. **Dor, ansiedade e depressão são preditivos para a pobre qualidade do sono em pacientes com carcinoma espinocelular de cabeça e pescoço** [tese]. Araçatuba: Faculdade de Odontologia da Universidade Estadual Paulista; 2023.

RESUMO

O sono desempenha um papel fundamental na regulação da homeostase dos sistemas imunológico e endócrino e na manutenção da ritmicidade circadiana. Pacientes com câncer exibem uma baixa qualidade do sono e uma ocorrência elevada de distúrbios do sono, que podem contribuir para a progressão tumoral. Além disso, dor e sintomas psicológicos são frequentes antes, durante e depois do tratamento oncológico. O objetivo deste estudo foi avaliar o valor preditivo das variáveis clinicopatológicas e psicológicas para a qualidade e desordens do sono em pacientes diagnosticados com carcinoma espinocelular de cabeça e pescoço (CECP). A qualidade e as desordens do sono foram avaliadas antes do início do tratamento oncológico por meio da aplicação dos questionários Índice de qualidade do sono de Pittsburgh, Índice de gravidade da insônia, Escala de sonolência de Epworth e STOP-Bang. Os sintomas de ansiedade e depressão foram avaliados por meio da Escala hospitalar de ansiedade e depressão (EADS). Análise univariada e regressão logística multivariada foram realizadas para avaliar os fatores preditores da qualidade e distúrbios do sono nos pacientes com CECP. Aproximadamente 50% de uma amostra de 132 pacientes com diagnóstico de carcinoma espinocelular localizados em boca, orofaringe e laringe apresentaram baixa qualidade de sono antes do início do tratamento oncológico. A ocorrência de insônia, sonolência diurna excessiva e alto risco de apnéia obstrutiva do sono foi observada em 19%, 15% e 54% dos pacientes com CECP, respectivamente. A análise univariada revelou associação da qualidade do sono reduzida com o estado civil “não casado”, consumo de tabaco, alcoolismo moderado e severo, dor e sintomas de ansiedade e depressão. A ocorrência de insônia foi associada à idade mais jovem e altos níveis de ansiedade, ao passo que a sonolência diurna excessiva foi relacionada a maior ocorrência de sintomas depressivos. Pacientes do sexo masculino e tabagistas atuais ou ex-tabagistas foram fatores associados ao alto risco de apneia do sono. A análise de regressão logística mostrou que a maior ocorrência de sintomas de ansiedade e a presença de dor foram preditivos para pior qualidade de sono antes do início do tratamento oncológico. Sintomas de ansiedade também foram fatores influenciadores independentes para menor qualidade subjetiva do sono, maior latência, menor eficiência, maior intensidade de disfunção diurna e insônia. A presença de dor influenciou independentemente a eficiência do sono. Além disso, maior ocorrência de sintomas depressivos foi associada à menor latência e menor duração do sono,

uso de medicamentos para dormir e ocorrência de sonolência diurna excessiva. Em conjunto, nossos resultados revelam que a dor relacionada ao tumor primário e sintomas de ansiedade e depressão são preditivos para baixa qualidade de sono nos pacientes com CECP. O presente estudo sugere que intervenções para redução de dor e manejo das desordens emocionais podem ter efeitos benéficos para melhorar a qualidade de sono em pacientes com câncer de cabeça e pescoço.

Palavras-chave: Neoplasia Maligna. Câncer de cabeça e pescoço. Sono. Qualidade do Sono. Ansiedade, Depressão.

Abstract

Valente GMK. **Pain, anxiety and depression are predictive of poor sleep quality in patients with head and neck squamous cell carcinoma** [thesis]. Araçatuba: Faculdade de Odontologia da Universidade Estadual Paulista; 2023.

ABSTRACT

Sleep plays a pivotal role in the regulation of homeostasis of the immune and endocrine systems and maintenance of circadian rhythmicity. Cancer patients display a poor sleep quality and increased occurrence of sleep disorders, which can contribute to tumor progression. Furthermore, primary tumor-related pain and psychological symptoms are also frequent before, during and after cancer treatment. The objective of this study was to evaluate the predictive value of clinicopathological and psychological variables for sleep quality and disorders in patients with head and neck squamous cell carcinoma (HNSCC). In the current study, sleep quality and disorders were assessed before starting oncological treatment through the questionnaires Pittsburgh Sleep Quality Index, Insomnia Severity Index, Epworth Sleepiness Scale, and STOP-Bang. Anxiety and depression symptoms were evaluated using the Hospital Anxiety and Depression Scale (HADS). Univariate analysis and multivariate logistic regression were performed to evaluate factors associated with sleep quality and disorders in HNC patients. The results showed that about 50% of a sample of 132 patients with tumors located in oral cavity, oropharynx and larynx display poor sleep quality before starting cancer treatment. The occurrence of insomnia, excessive daytime sleepiness and high risk of obstructive sleep apnea was observed in 19%, 15% and 54% of HNSCC patients, respectively. Univariate analysis revealed association of the reduced sleep quality with marital status “non-married”, tobacco consumption, moderate and healthy drinker, tumor-related pain and anxiety and depression symptoms. The occurrence of insomnia was associated with younger age and higher levels of anxiety, while excessive daytime sleepiness was related to increased occurrence of depressive symptoms. Male patients and current or former smoker were factors associated with a high risk of sleep apnea. Logistic regression analysis showed that higher levels of anxiety symptoms and presence of pain were predictive of poor sleep quality prior to cancer treatment. Higher occurrence of anxiety symptoms were also independent influencing factors for decreased subjective sleep quality, higher sleep latency, lower efficiency, and increased intensity of daytime dysfunction and insomnia. The occurrence of pain independently influenced sleep efficiency. Moreover, higher occurrence of depression symptoms was associated with lower latency and shorter sleep duration, use of sleep medication and occurrence of excessive daytime sleepiness. Taken together, our results reveal that primary tumor-related pain and anxiety and

depression symptoms are predictive of poor sleep quality in HNSCC patients. The current study suggests that interventions to reduce pain and management of emotional symptoms can benefit sleep quality in head and neck cancer patients.

Keywords: Malignant neoplasia. Head and neck cancer. Sleep. Sleep quality. Anxiety. Depression.

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Lista de Abreviaturas

LISTA DE ABREVIATURAS

BMI	Body Mass Index
CCI	Charlson comorbidity index
CECP	Carcinoma espinocelular de cabeça e pescoço
CI	Confidence interval
CNS	Central Nervous System
EADS	Escala hospitalar de ansiedade e depressão
EDS	Excessive daytime sleepiness
ESS	Epworth Sleepiness Scale
GABA	Gamma-Aminobutyric Acid
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale-Anxiety
HADS-D	Hospital Anxiety and Depression Scale-Depression
HNC	Head and Neck Cancer
HNSCC	Head and Neck Squamous Cell Carcinoma
HPA	Hypothalamus-Pituitary-Adrenal
IL1β	Interleukin-1β
IL6	Interleukin-6
ISI	Insomnia Severity Index
N	Nodal metastasis
non-REM	non-Rapid Eye Moviment
OR	Odds ratio
OSA	Obstructive sleep apnea
OSCC	Oral Squamous Cell Carcinoma
PSQI	The Pittsburgh Sleep Quality Index
REM	Rapid Eye Moviment
SD	Standard deviation
T	Primary tumor size
UICC	Union for International Cancer Control

Sumário

Sumário

Title: Pain, anxiety and depression are predictive of poor sleep quality in patients with head and neck squamous cell carcinoma*

Giseli Mitsuy Kayahara,[1,2] Bruna Amélia Moreira Sarafim-Silva,[1] Vitor Bonetti Valente,[1,2] Éder Ricardo Biasoli,[1] Glauco Issamu Miyahara,[1,2] Daniel Galera Bernabé,[1,2]

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1 INTRODUCTION

Sleep is crucial to human survival by participating in the regulation of immune and endocrine systems playing a key role in cognitive and brain functions [1,2]. Cancer patients have increased occurrence of sleep-related disorders compared to non-cancer individuals [3]. Poor sleep quality is self-reported by 45–80% of cancer patients versus 29–32% of the healthy population [4-7] and has been associated with tumor progression [8,9]. Changes in sleep pattern and quality may affect cancer prognosis. Both short (≤6h) and long (≥10h) sleep durations were associated with higher mortality rate in advanced cancer patients [10]. Stone et al. [11] showed in a meta-analysis that long sleep duration was also associated with cancer-specific mortality for lung cancer individuals and all-cause mortality in breast tumor patients. On the other hand, cancer-induced changes in sleep pattern have also been investigated. Cytokines and growth factors secreted in the tumor microenvironment may reach the central nervous system (CNS) [12,13] disrupting the behavior and sleep in humans [14]. For example, IL6 and IL1β are cytokines released by tumor and inflammatory cells to promote cancer progression. These same molecules can act systemically and contribute to the development of sleep disorders [14,15].

Insomnia, excessive daytime sleepiness and obstructive sleep apnea (OSA) are disorders that can affect patients at different stages of cancer treatment. Previous studies showed that insomnia is about 2-times more common among cancer patients than in the non-cancer population and its severity may be related to chemotherapy or radiotherapy [16-19]. Advanced clinical stage is associated with tiredness and lack of energy, resulting in increased daytime sleepiness in cancer patients [20]. Furthermore, in these patients, daytime sleepiness can be linked to OSA and side effects of treatment [21]. In cancer patients, sleep disorders are related to increased occurrence of pain, fatigue, depression and poorer quality of life [22-23]. Pain and psychological disorders such as anxiety and depression can influence sleep quality through hypothalamus-pituitary-adrenal (HPA) axis activation [24-25]. A study of our team showed that pain related to the primary tumor was associated with increased systemic cortisol levels in patients with oral squamous cell carcinoma (OSCC) [26]. In this context, both flatter cortisol slope and pain were significant predictors of poor sleep quality in cancer patients [27-28]. Moreover, the simultaneous occurrence of pain and sleep disturbances has been correlated with lower quality of life from individuals undergoing chemotherapy [29]. Cancer patients often display elevated levels of anxiety throughout the diagnosis and treatment processes. Fontes et al. [30] revealed a high incidence of poor sleep quality in breast cancer women with higher levels of anxiety and depression. Furthermore, a recent study demonstrated that together pain,

anxiety and depression were also independent influencing of poor sleep in cancer patients throughout the treatment [31]. However, further studies are needed to investigate the relationship between pain, psychological symptoms and sleep quality previously to oncology treatment.

Head and neck cancer (HNC) is the 6th most common cancer worldwide [32], with oral and oropharyngeal tumors being the main subtypes [33]. Globally, oral and oropharyngeal squamous cell carcinoma affect approximately 476,125 people annually [32]. The main risk factors to head and neck squamous cell carcinoma (HNSCC) occurrence are chronic tobacco use and alcohol consumption [33]. Sleep quality and its influencing factors have been investigated in HNC patients [34-36]. For instance, after completing treatment, about a third of HNC patients display poor sleep quality [37]. Shuman et al. [35] demonstrated that are pain, xerostomia, depression, presence of a tracheotomy tube, comorbidities, and younger age the main predictors of worse sleep one year after HNC diagnosis. On the other hand, about 44% of newly diagnosed HNC individuals display a poor sleep quality [34]. In these patients, the worse sleep quality has been associated with younger age, female sex, passive coping style, oral pain, and less sexual interest [34]. Despite the evidence of the relationship between some clinicopathological features and sleep quality, no study has assessed whether biobehavioral and psychological variables can be risk factors of sleep disorders in HNC patients. In the current study, we characterize the pretreatment sleep pattern of HNSCC patients and its association with clinicopathological and psychological variables.

2 PATIENTS AND METHODS

2.1 Ethics statement

This study was approved by the Committee of Human Studies of the São Paulo State University (UNESP), School of Dentistry, Araçatuba, SP, Brazil (Protocol number, 52975221.6.0000.5420). Informed consent was obtained from all patients included in the research.

2.2 Patients

HNSCC patients were recruited from Oral Oncology Center, São Paulo State University (UNESP), School of Dentistry, Araçatuba, SP, Brazil, between 2020 and 2023. Patients were eligible if they had histopathological diagnosis of HNSCC with tumors located in the tongue, floor of the mouth, retromolar area, gingiva, hard palate, buccal mucosa, lower lip, soft palate, tonsil, tongue base or larynx. Patients with history of cancer and cognitive deficits that could interfere with the understanding of the questionnaires were excluded from study.

2.3 Demographic, clinicopathological and biobehavioral variables

Sociodemographic, clinicopathological and behavioral data were extracted from the medical records. Sociodemographic (age, sex, marital status, and education level), clinicopathological (occurrence of comorbidities, tumor location, primary tumor size (T), nodal metastasis (N), clinical staging, and biobehavioral (tobacco and alcohol consumption) variables were obtained in patients' admission. The occurrence and severity of comorbidities were evaluated according to the Charlson comorbidity index (CCI) [38]. Clinical staging was determined according to the Union for International Cancer Control (UICC) criteria. Tobacco and alcohol consumption were evaluated as follows: non-smoker/non-drinker, light (up to 10 cigarettes or 1-2 drinks per day), moderate (11-20 cigarettes or 3-4 drinks per day), and heavy (more than 20 cigarettes or more than 4 drinks per day) use [39].

2.4 Sleep quality

The Pittsburgh Sleep Quality Index (PSQI) validated for Brazilian Portuguese was used to assess the sleep quality of HNSCC patients before starting treatment [40]. The reliability of PSQI has been confirmed in the general population [41,42] and in cancer patients [34,42,43]. PSQI contains 19 items for the purpose of evaluating seven domains related to sleep quality: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medication and daytime dysfunction. Each domain is assessed on a three-point scale (0 to 3 points). Scores from all domains were summed to reach the PSQI global score that ranges from 0 to 21, with a score of more than 5 being indicative of poor sleep quality [44].

2.5 Assessment of symptoms of anxiety and depression

The insomnia severity was measured by the instrument Insomnia Severity Index (ISI). The ISI was validated to cancer patients [17] and comprises seven items that are rated using a five-point Likert scale. A global score obtained from the sum of all items ranges between 0 to 28. Scores lower than 8 indicate absence of insomnia, while scores ≥8 indicate its occurrence [45]. ISI was adapted and validated for Brazilian Portuguese by Castro et al. [46] with a sensitivity rate of 73% and specificity of 80% in general population.

2.6 Daytime sleepiness

The Epworth Sleepiness Scale (ESS) was applied to assess excessive daytime sleepiness (EDS) in HNSCC patients [40,47]. ESS consists of eight questions in which the individuals are asked to assess their likelihood of falling asleep or dozing, while performing different daytime activities. The questions are scored on a four-point scale from 0 (“would never doze”) to 3 (“high chance of dozing”). The global score ranges between 0 to 24, with increased scores representing higher sleepiness. A total ESS score greater than 10 suggests pathological daytime sleepiness [47].

2.7 Risk of obstructive sleep apnea

The risk of obstructive sleep apnea (OSA) in HNSCC patients was evaluated by STOP-Bang questionnaire [48-50]. STOP-Bang is composed of eight questions with dichotomous answers (yes or no). The STOP portion aims to evaluate snoring, tiredness, observed apnea, arterial hypertension, while Bang portion is applied to evaluate the body mass index (BMI) (>35 kg/m2), age (>50 years-old), neck circumference (>40cm) and sex [48]. A score of 1 was assigned for each affirmative answer. Patients scoring 0 to 2 were considered as having a low risk of OSA and those with a score higher than 2 as having a high risk.

2.8 Assessment of symptoms of anxiety and depression

The occurrence and severity of anxiety and depression symptoms were evaluated by the Hospital Anxiety and Depression Scale (HADS) [51]. This scale was validated for Brazilian Portuguese by Pais-Ribeiro et al. [52]. The HADS contains 14 items divided into two subscales. Each subscale has seven questions to assess anxiety (HADS-A) and depression (HADS-D) symptoms that are scored separately [51,53]. Each item is scored on a scale from 0 to 3, with a total score ranging from 0 to 21 in each subscale. The HADS has been widely used for cancer patients having a satisfactory internal consistency [54].

2.9 Statistical analysis

SPSS software (version 24.0 software IBM Corp., Armonk, NY, USA) was used to perform all statistical analyses. Overall sleep quality was defined as good or poor when HNSCC patients displayed a score of ≤5 or higher than 5, respectively. Each PSQI domain was analyzed as a dichotomic measure according to the occurrence of the event. Each domain was assessed on a three-point scale (0 to 3 points). To statistical analysis, PSQI domains were considered as a binary measure, grouping scores 0 and 1 (improved subjective sleep quality, lower sleep latency, higher sleep duration, higher sleep efficiency, decreased sleep disturbance, lower use of sleep medication and lower diurnal dysfunction), and 2 and 3 (worse subjective sleep quality, higher sleep latency, lower sleep duration, lower sleep efficiency, increased sleep disturbance, higher use of sleep medication and higher diurnal dysfunction). Sleep disorders were also evaluated as dichotomic measure. For insomnia severity, score lower than 8 in the ISI was

considered as absence of insomnia while those ≥ 8 indicated some level of insomnia. ESS scores were classified as absence (score up to 10) or occurrence (score higher than 10) of EDS. OSA risk was defined as low and high when STOP-Bang scores ranged from 0 to 2 and 3 to 8, respectively. The median of the HADS global score was used as cut-off to stratify the anxiety and depression levels. The HADS-A and HADS-D scores below and above the median defined lower and higher levels of anxiety and depression symptoms, respectively. Chi-square and Fisher's exact tests were applied to assess the relationship between overall sleep quality, PSQI domains, insomnia severity, EDS and risk of OSA and demographic and clinicopathological features, as well as symptoms of anxiety and depression. Only those variables with $p \leq 0.2$ in the univariate analysis were considered in the regression models. Multivariate regression analysis was made using the stepwise logistic regression method. The analyses were carried out considering sleep quality, insomnia, and EDS as response variables, and the demographic, clinicopathological, and psychological features were explanatory variables. To assess the predictive factors of OSA, the explanatory variables were only demographic and clinicopathological data. Symptoms of anxiety and depression were not included in the regression model because their occurrence is subsequent to the occurrence of the risk factors for OSA assessed by STOP-Bang instrument. To evaluate the bidirectional relationship of sleep with pain and psychological symptoms, another regression model was performed. In this case, pain and levels of anxiety and depression symptoms were considered as response variables and sleep quality and disorders were exploratory variables. Significance level was set at 5% ($p < 0.05$) for all analyses.

3 RESULTS

3.1 Epidemiological and clinicopathological profile

One hundred and thirty-two patients diagnosed with HNSCC were included in the current study, of whom 79 (59.8%) had tumors located in oral cavity, 42 (31.8%) in oropharynx and 11 (8.3%) in larynx. Their sociodemographic and clinicopathological features are shown in Table 1. Most HNSCC patients were men (77.3%), with mean age of 63.98 years, white (56.5%), married (53.8%) and had a family income of R$ 1000–5000 (1 USD=5 reais, approximately) per month (51.4%). Forty percent of HNSCC patients exhibited overweight or obesity (BMI) ≥ 25kg/m2) at the time of diagnosis and 80% had at least 1 type of comorbidity. The main comorbidities observed in HNSCC patients were hypertension (43.2%), gastritis (20.5%) and diabetes (15.9%). About 37% of HNSCC patients had nodal metastasis at the time of diagnosis and 59.6% displayed advanced clinical staging. Tumor-related pain was reported as moderate by 14.6% of patients, followed by 10.6% with mild pain and 9.8% with severe pain. Data concerning education, tobacco and alcohol consumption, comorbidities index, T classification, and anxiety and depression symptoms are also shown in Table 1.

Table 1 Demographic and clinicopathological profile of HNSCC patients

Variable	HNSCC patients n (%)
Sex	
Men	102 (77.3)
Women	30 (22.7)
Age (years)	
Mean (SD)	63.98 (0.94)
Age range	
0-45y	9 (6.8)
46-65y	56 (42.4)
>65y	67 (50.8)
Ethnicity*	
Non-White	57 (43.5)
White	74 (56.5)
Marital status	
Single	26 (19.7)
Married	71 (53.8)
Divorced	24 (18.2)
Widowed	11 (8.3)
Education	
Illiterate	9 (6.8)
Elementary school or less	89 (67.4)
High school	20 (15.2)
University	14 (10.6)

Familiar income (R$/month)*	
R$0/mo	4 (3.9)
<R$1000/mo	1 (44.7)
R$1000-5000/mo	53 (51.4)
>R$5000/mo	0 (0)
Primary tumor location*	
Oral cavity	79 (59.8)
Oropharynx	42 (31.9)
Larynx	11 (8.3)
Comorbidity	
No	26 (19.7)
Yes	106 (80.3)
CCI score	
0	65 (49.2)
1	41 (31.1)
2	16 (12.9)
3	9 (6.8)
Comorbidity type	
Hypertension	57 (43.2)
Gastritis	27 (20.5)
Diabetes	21 (15.9)
Depression	13 (9.9)
BMI*	
Under weight	20 (15.6)
Normal weight	76 (59.4)
Overweight or obesity	52 (40.6)
Smoking	
No	18 (13.6)
Current smoker	89 (67.5)
Former smoker	25 (18.9)
Tobacco intensity*	
Light	39 (29.8)
Moderate	38 (29.0)
Heavy	36 (27.6)
Alcohol consumption	
None	20 (15.2)
Current drinker	65 (49.2)
Former drinker	47 (35.6)
Alcohol intensity*	
Light	27 (20.6)
Moderate	19 (14.5)
Heavy	65 (49.7)
T classification*	
T1	32 (24.6)
T2	29 (22.3)
T3	42 (32.3)
T4	27 (20.8)
Regional metastasis*	
N0	82 (63.1)

N+	48 (36.9)
Clinical stage*	
I	29 (22.1)
II	24 (18.3)
III	34 (26.0)
IV	44 (33.6)
Tumor-related pain*	
No	79 (63.7)
Yes	45 (36.3)
Pain severity	
Mild	13 (10.6)
Moderate	18 (14.6)
Severe	12 (9.8)
HADS-A*	
No	89 (74.2)
Possible	18 (15.0)
Probable	13 (10.8)
HADS-D*	
No	96 (80.0)
Possible	13 (13.3)
Probable	8 (6.7)

Abbreviation, SD, Standard deviation; CCI, Charlson Comorbidity Index.
*Variables with missing data.

3.2 Characterization of sleep quality and disorders in patients with HNSCC

The sleep quality and disorders of HNSCC patients were evaluated before starting cancer treatment using the PSQI, ISI, ESS and STOP-Bang questionnaires. The average of PSQI global score was 6.752 ± 0,363 (ranging from 1 to 18). Sixty-four patients (49.6%) were classified as having a poor sleep quality (Table 2). Interestingly, among patients classified as poor sleepers (n=64), 56.2% considered their sleep as “very good” or “good”. On the other hand, considering the patients classified as good sleepers (n=65), only 3% considered their sleep “bad” or “very bad”. HNSCC patients took an average of 27 ± 3.145 min to fall asleep and slept an average of 6.5 ± 0.155 hours per night. Most patients reported having a good subjective sleep quality (70.2%) (Table 2). Sixty percent of them fell asleep within 30 minutes and about 70% were able to sleep 7 hours or more per night (Table 2). The sleep efficiency was higher than 75% for most patients with HNSCC (64.1%) (Table 2). Almost all patients displayed some level of sleep disturbance measured by PSQI (98.5%). The majority did not use sleep medication during the last month (85.5%) and did not report any daytime dysfunction (72.5%) (Table 2). When we assessed the insomnia symptoms obtained from ISI, only 24 HNSCC patients (19.2%)

reported some level of insomnia while EDS measured by ESS was experienced by about 15% from patients (Table 2). More than 54% of HNSCC patients were classified as having a high risk of OSA development whereas 45.6% had a low risk (Table 2).

Table 2 Sleep quality and disorders of HNSCC patients

Sleep features	HNSCC n (%)
Overall sleep quality[a]	
Good sleeper (score ≤5)	65 (50.4)
Poor sleeper (score >5)	64 (49.6)
Subjective sleep quality[a]	
Very good	9 (6.9)
Good	92 (70.2)
Bad	23 (17.6)
Very bad	7 (5.3)
Sleep latency, in minutes[a]	
≤ 15 minutes	48 (36.6)
16 – 30 minutes	31 (23.7)
31 – 60 minutes	31 (23.7)
>60 minutes	21 (16)
Sleep duration, in hours[a]	
> 7 hours	42 (32.8)
6 – 7 hours	47 (36.7)
5 – 6 hours	22 (17.2)
<5 hours	17 (13.3)
Sleep efficiency[a]	
> 85%	65 (50.8)
75 – 84%	17 (13.3)
65 – 74%	19 (14.8)
<65%	27 (21.1)
Sleep disturbances[a]	
None (0)	2 (1.5)
Minimun (1-9)	87 (66.4)
Moderate (10-18)	41 (31.3)
Severe (19-21)	1 (0.8)
Use of sleep medication[a]	
Not during the past month	112 (85.5)
Less than once a week	2 (1.5)
Once or twice a week	0 (0)
Three or more times a week	17 (13)
Daytime dysfunction[a]	
None (0)	95 (72.5)
Minimum (1-2)	18 (13.7)
Moderate (3-4)	11 (8.4)
Severe (5-6)	7 (5.4)

Insomnia[b]	
No	101 (80.8)
Yes	24 (19.2)
Excessive Daytime Sleepiness[c]	
No	107 (84.9)
Yes	19 (15.0)
Risk of OSA[d]	
Low	57 (45.6)
High	68 (54.4)

[a]Sleep features evaluated by Pittsburgh Sleep Quality Index.
[b]Insomnia severity was measured by Insomnia Severity Index Questionnaire.
[c]Daytime sleepiness was evaluated by Epworth Sleepiness Scale Questionnaire.
[d]Risk of OSA was measured using the STOP-Bang Questionnaire.

3.3 Associations between sleep quality and clinicopathological and psychological variables

Univariate analysis showed that occurrence of regional metastasis was associated with pain (p=0.001) and use of analgesic (p=0.006) in HNSCC patients. Married patients exhibited an improved overall sleep quality in comparison with non-married (p=0.032) (Table 3). Former smokers showed good overall sleep quality when compared to current smokers (p=0.028). Similarly, mild drinkers had good sleep quality when compared to non-drinkers (p=0.009) (Table 3). On the other hand, pain related to the primary tumor was associated with poor sleep quality in HNSCC patients (p=0.048) (Table 3). When the associations between the clinicopathological variables and PSQI domains were analyzed, we observed that more former smokers' patients classified their subjective sleep quality as being "bad" or "very bad" (p=0.035) than non-smokers and current smokers who more frequently reported a "very good" or "good" sleep (Table 3). Furthermore, shorter sleep duration was associated with moderate alcoholism (p=0.035). HNSCC patients with tumor-related pain displayed lower sleep efficiency (less than 75%) compared to patients who did not report pain (p=0.006) (Table 3). Regarding sleep disturbances, mild drinkers had lower occurrence of sleep-related disorders than moderate and healthy drinkers (p=0.011) (Table 3). HNSCC men used sleeping medication less frequently than women (p=0.017). Similarly, current drinkers consumed sleep-inducing medication with less frequency when compared with non-drinkers and former drinkers' patients (p=0.002) (Table 3). Moreover, male patients (p=0.025) and current smokers (p=0.031) had lower intensity of daytime dysfunction than women and non-smokers or former smokers, respectively. Likewise, moderate drinkers also displayed lower intensity of daytime dysfunction compared to non-drinkers (p=0.003) (Table 3). Concerning sleep disorders, the occurrence of insomnia was associated with younger age (p=0.011). In HNSCC patients, being male, current or former smoker and being heavy smoker were linked to high risk of OSA, while woman and non-smokers displayed a low risk. No relationship was observed between clinicopathological variables and daytime sleepiness in our sample. Likewise, no association was found between sleep quality and disorders and T classification, nodal metastasis and clinical staging from HNSCC patients (p>0.05).

We also assessed the relationship between the psychological variables and sleep quality and disorders in HNSCC patients. When association between anxiety and PSQI domains was assessed, patients with higher levels of anxiety symptoms displayed worse subjective sleep quality (p=0.016), higher sleep latency (p=0.015), shorter sleep duration (p=0.049), low-

efficiency sleep (p=0.009), and increased severity of sleep disturbances (p=0.044) than those patients with lower anxiety (Table 3). Although HNSCC patients highly anxious displayed increased intensity of daytime dysfunction, this result did not reach significance (p=0.051) (Table 3). Increased levels of anxiety were also related to the occurrence of insomnia symptoms measured by ISI (p=0.002) (Table 3). Higher levels of depression symptoms in HNSCC patients were associated with increased sleep latency (p=0.002), more frequent use of sleeping medication (p=0.017), increased occurrence of sleep disorders (p=0.005), and daytime dysfunction (p=0.017) (Table 3). Higher occurrence of depression symptoms was linked to daytime sleepiness (p=0.009) and high risk of OSA (p=0.020) evaluated from ESS and STOP-Bang questionnaires, respectively (Table 3).

Table 3 Associations between demographic, clinicopathological, and psychological variables and the sleep quality and disorders in HNSCC patients from the univariate analysis

Variable[a]	Sex	Age	Marital status	Tobacco consumption	Tobacco intensity	Alcohol consumption	Alcohol intensity	Tumor-related pain	HADS-A	HADS-D
Overall Sleep quality	0.481	0.934	0.032[b,e]	0.028[b,c]	0.748	0.135	0.009[b,d]	0.048[b]	0.010[b,f]	<0.0001[b,f]
Subjective sleep quality	0.370	0.259	0.146	0.035[b,c]	0.555	0.663	0.310	0.322	0.016[b,f]	0.138
Sleep latency	0.436	0.849	0.385	0.304	0.796	0.354	0.101	0.548	0.015[b,f]	0.002[b,f]
Sleep duration	0.445	0.398	0.087	0.171	0.616	0.322	0.035[b,d]	0.492	0.049[b,f]	0.280
Sleep efficiency	0.518	0.848	0.456	0.335	0.569	0.136	0.086	0.006[b]	0.009[b,f]	0.143
Sleep disturbances	0.173	0.909	0.135	0.082	0.145	0.735	0.011[b,d]	0.097	0.044[b,f]	0.005[b,f]
Use of sleep medication	0.017[b]	0.441	0.379	0.129	0.263	0.002[b,c]	0.078	0.365	0.514	0.017[b,f]
Daytime dysfunction	0.025[b]	0.580	0.526	0.031[b,c]	0.017[b,d]	0.011[b,c]	0.003[b,d]	0.354	0.051	0.017[b,f]
Insomnia	0.176	0.011[b]	0.297	0.163	0.202	0.738	0.178	0.301	0.002[b]	0.063
Daytime sleepiness	0.386	0.961	0.097	0.883	0.796	0.788	0.261	0.420	0.222	0.009[b,f]
Risk of OSA	0.002[b]	0.079	0.283	<0.0001[b,c]	0.005[b]	0.341	0.274	0.259	0.056	0.020[b,f]

Abbreviation; HNSCC, head and neck squamous cell carcinoma; HADS-A, Hospital Anxiety and Depression Scale-Anxiety; HADS-D, Hospital Anxiety and Depression Scale-Depression; OSA, Obstructive Sleep Apnea.

[a]The variables' associations with the domains of sleep quality or disorders reached statistical significance.

[b]Values were considered statistically significant at $p<0.05$ (Chi-square test or Fisher's exact test).

[c]No alcohol/tobacco consumption, current drinker/smoker, or ex-drinker/smoker.

[d]Values were measured with the intensity categories (none, mild, moderate, or intense).

[e]Values were measured with the binary measure (non-married and married).

[f]Values were measured with the binary measure (lower and higher).

3.4 Higher levels of pain and anxiety are predictive of poor sleep quality in HNSCC

To identify variables that affect pretreatment sleep quality and disturbances in HNSCC patients, logistic regression analyses were performed. Multivariate analysis showed that regional metastasis at the time of diagnosis was predictive of good overall sleep quality (odds ratio (OR), 3.246; 95% confidence interval (CI), 1.062 – 9.900 p=0.039), even after adjustment for possible confounding variables (OR, 3.144; 95% CI, 1.034 – 7.246; p=0.044) (Table 4). HNSCC patients that displayed pain related to the primary tumor were about 6 times more likely to have poor sleep quality, compared to those patients without pain (unadjusted model, OR, 6.407; 95% CI, 2.054 – 19.987; p=0.001; adjusted model, OR, 6.448; 95% CI, 2.078 – 20.013; p=0.001) (Table 4). Tumor-related pain also affected sleep efficiency. Patients with pain showed 4 times higher risk of having low-efficiency sleep (efficiency <75%) than pain-free patients (OR, 3.728; 95% CI, 1.426 – 9.743; p=0.007). This result remained significant even after adjustment (OR, 3.867; 95% CI, 1.477 – 10.124; p=0.006) (Table 4). Furthermore, a bidirectional relationship between pain and sleep quality was observed. HNSCC patients with poor sleep quality had 2.5-fold more chances of showing primary tumor-related pain (OR,2.510; 95% CI, 1.100 – 5.727; p=0.029), even after adjustment for confounding variables (OR, 3.875; 95% CI, 1.527 – 9.833; p=0.004) (Table S1). In the regression model that aimed to evaluate the factors associated with the development of sleep apnea, only tobacco intensity was predictive of high risk of OSA. HNSCC patients who were light (unadjusted model, OR, 9.722; 95% CI, 2.340 – 40.396; p=0.002) moderate (unadjusted model, OR, 4.941; 95% CI, 1.204 – 20.283; p=0.027), or heavy (unadjusted model, OR, 8.167; 95% CI, 1.945 – 34.282; p=0.004) tobacco smokers had 9.7, 4.9 and 8.1-times more likely to display high risk of OSA than non-smokers patients. However, after adjustment for medications that can induce sleepiness, tobacco intensity did not remain in the regression model.

Psychological variables were associated with poor sleep quality and sleep disorders. The risk of having a worse overall sleep quality was 5.8 times increased among patients with increased levels of anxiety compared to patients with lower levels of anxiety (unadjusted model, OR, 5.847; 95% CI, 2.045 – 16.719; p=0.001; adjusted model, OR, 5.575; 95% CI, 1.946 – 15.971; p=0.001) (Table 5). Increased levels of anxiety measured by HADS-A were also predisposing factors of worse subjective sleep quality (unadjusted model, OR, 2.896 95% CI, 1.150 – 7.293 p=0.024) and higher sleep latency (time to fall asleep higher than 30 min)

(unadjusted model, OR, 2.336; 95% CI, 1.016 – 5.373; p=0.046) (Table 5). Nevertheless, when the regression model was adjusted for use of medications that can induce sleepiness, the anxiety levels did not remain in the final model which had subjective sleep quality and latency as dependent variables. HNSCC patients showing higher levels of anxiety had 4.5 times more chances of have low-efficiency sleep (efficiency lower than 75%) (OR, 4.561; 95% CI, 1.758 – 11.835; p=0.002) (Table 5). This result was kept even in the adjusted model (OR, 4.346; 95% CI, 1.671 – 11.307; p=0.003) (Table 5). Before starting oncology treatment, the risk of display daytime dysfunction moderate and intense was about 6 times greater in those patients highly anxious compared to low-anxious (unadjusted model, OR, 6.074; 95% CI, 1.361 – 27.113; p=0.018; adjusted model, OR, 6.164; 95% CI, 1.384 – 27.460; p=0.017) (Table 5). Anxiety symptoms were also related to insomnia. HNSCC patients with higher levels of anxiety had a 6-fold increase in the chance of displaying insomnia than those with lower levels of anxiety (unadjusted model, OR, 6.158; 95% CI, 1.928 – 19.670; p=0.002; adjusted model, OR, 6.324; 95% CI, 1.978 – 20.225; p=0.002).

Depression symptoms did not remain in the regression model that had overall sleep quality as a dependent variable. However depression symptoms influenced parameters related to sleep quality. HNSCC patients that have experienced higher levels of depressive symptoms were about 3 times more likely to show increased sleep latency (unadjusted model, OR, 3.104; 95% CI, 1.357 – 7.100; p=0.007; adjusted model, OR, 3.574; 95% CI, 1.617 – 7.898; p=0.002) and shorter sleep duration (unadjusted model, OR, 3.598; 95% CI, 1.242 – 10.424; p=0.018; adjusted model, OR, 3.736; 95% CI, 1.286 – 10.853; p=0.015) (Table 5). As expected, higher levels of depression were also associated with the use of sleep medication. Patients with higher levels of depressive symptoms exhibited 3.6 times higher risk of consuming sleep-inducing medication than those with low levels of depression in unadjusted (OR, 3.680; 95% CI, 1.007 – 13.449; p=0.049). When the model was adjusted for BMI this relationship was lost (OR, 3.574; 95% CI, 0.979 – 13.046; p=0.054) (Table 5). In the multivariate logistic regression analysis, elevated levels of depressive symptoms in HNSCC patients were associated with a 2-fold increased chance of EDS (unadjusted model, OR, 2.778; 95% CI, 1.250 – 6.174; p=0.012; adjusted model, OR, 4.076; 95% CI, 1.342 – 12.377; p=0.013) (Table 5). On the other hand, sleep quality, insomnia and daytime sleepiness also predicted psychological symptoms, revealing a cross-talk between sleep and emotional status in HNSCC patients. Poor sleep quality was associated with higher levels of anxiety (unadjusted model, OR, 2.559; 95% CI, 1.215 – 5.392; p=0.013; adjusted model, OR, 2.490; 95% CI, 1.180 – 5.256; p=0.017) and depression symptoms (unadjusted model, OR, 3.364; 95% CI, 1.513 – 7.479; p=0.003; adjusted model,

OR, 3.259; 95% CI, 1.462 – 7.263; p=0.004) measured before starting treatment in HNSCC patients. While HNSCC patients with insomnia were about 5-times more likely to exhibit elevated levels of anxiety symptoms (unadjusted model, OR, 4.860; 95% CI, 1.664 – 14.195; p=0.004; adjusted model, OR, 4.985; 95% CI, 1.705 – 14.576; p=0.003), EDS was associated with higher levels of depressive symptoms (unadjusted model, OR, 3.900; 95% CI, 1.280 – 11.885; p=0.017; adjusted model, OR, 4.011; 95% CI, 1.315 – 12.241; p=0.015) (Table S1).

Table 4 Results from a stepwise logistic regression analysis considering the demographic and clinicopathological data as independent variables and the PSQI measures as response variables in patients with HNSCC

Dependent variables	Independent variables											
	Regional metastasis[a]				Pain[a]				Tobacco intensity[a]			
	OR unadjusted (95% CI)	p-value	OR adjusted[b] (95% CI)	p-value	OR unadjusted (95% CI)	p-value	OR adjusted[b] (95%CI)	p-value	OR unadjusted (95% CI)	p-value	OR adjusted[b] (95%CI)	p-value
Sleep efficiency	-	-	-	-	3.728 (1.426 – 9.743)	0.007	3.867 (1.477 – 10.124)	0.006	-	-	-	-
Overall Sleep quality	- 3.246 (1.062 – 9.900)	0.039	- 3.144 (1.034 – 7.246)	0.044	6.407 (2.054 – 19.987)	0.001	6.448 (2.078 – 20.013)	0.001	-	-	-	-
Risk of OSA	-	-	-	-	-	-	-	-	9.722[c] (2.340 – 40.396)	0.002	-	-
									4.941[d] (1.204 – 20.283)	0.027	-	-
									8.167[e] (1.945 – 34.282)	0.004	-	-

Abbreviations; OR, Odds ratio; CI, Confidence interval; HADS-A, Hospital Anxiety and Depression Scale-Anxiety; HADS-D, Hospital Anxiety and Depression Scale-Depression.
The demographic variables were sex, age, marital status, family income and education.
The clinicopathological variables were comorbidity, primary tumor-related pain, tumor location, T classification, regional metastasis, clinical staging, tobacco and alcohol consumption.
[a]These variables remained in the final regression model.
[b]Values were adjusted for sex, age, marital status, comorbidity, tobacco and alcohol consumption, use of medications that affect sleep and BMI.
[c]Mild smokers vs non-smokers
[d]Moderate smokers vs non-smokers
[e]Healthy smokers vs non-smokers
All values are considered statistically significant at $p<0.05$

Table 5 Results from a stepwise logistic regression analysis considering the psychological data as independent variables and the PSQI measures as response variables in HNSCC patients

Dependent variables	Independent variables							
	HADS-A[a]				HADS-D[a]			
	OR unadjusted (95% CI)	p-value	OR adjusted[b] (95% CI)	p-value	OR unadjusted (95% CI)	p-value	OR adjusted[b] (95% CI)	p-value
Overall Sleep quality	5.847 (2.045 – 16.719)	0.001	5.575 (1.946 – 15.971)	0.001	-	-	-	-
Subjective sleep quality	2.896 (1.150 – 7.293)	0.024	-	-	-	-	-	-
Sleep latency	2.336 (1.016 – 5.373)	0.046	-	-	3.104 (1.357 – 7.100)	0.007	3.574 (1.617 – 7.898)	0.002
Sleep duration	-	-	-	-	3.598 (1.242 – 10.424)	0.018	3.736 (1.286 – 10.853)	0.015
Sleep efficiency	4.561 (1.758 – 11.835)	0.002	4.346 (1.671 – 11.307)	0.003	-	-	-	-
Use of sleep medication[c]	-	-	-	-	3.680 (1.007 – 13.449)	0.049	3.574 (0.979 – 13.046)	0.054
Daytime dysfunction	6.074 (1.361 – 27.113)	0.018	6.164 (1.384 – 27.460)	0.017	-	-	-	-
Insomnia	6.158 (1.928 – 19.670)	0.002	6.324 (1.978 – 20.225)	0.002	-	-	-	-
Daytime sleepiness	-	-	-	-	2.778 (1.250 – 6.174)	0.012	4.076 (1.342 – 12.377)	0.013

Abbreviations; OR, Odds ratio; CI, Confidence interval; HADS-A, Hospital Anxiety and Depression Scale-Anxiety; HADS-D, Hospital Anxiety and Depression Scale-Depression.

[a]These variables remained in the final regression model.

[b]Values were adjusted for sex, age, marital status, comorbidity, tobacco and alcohol consumption, use of medications that affect sleep and BMI.

[c]Use of sleep medication was adjusted for sex, age, marital status, comorbidity, tobacco and alcohol consumption and BMI.

All values are considered statistically significant at $p<0.05$.

Table S1 Results from a stepwise logistic regression analysis considering the sleep quality and disorders as independent variables and symptoms of anxiety and depression as explanatory variables in patients with HNSCC

Dependent variables	Independent variables											
	Overall sleep quality[a]				Insomnia[a]				Excessive daytime sleepiness[a]			
	OR unadjusted (95% CI)	p-value	OR adjusted[b] (95% CI)	p-value	OR unadjusted (95% CI)	p-value	OR adjusted[b] (95% CI)	p-value	OR unadjusted (95% CI)	p-value	OR adjusted[b] (95% CI)	p-value
Pain	2.510 (1.100 – 5.727)	0.029	3.875 (1.527 – 9.833)	0.004	-	-	-	-	-	-	-	-
HADS-A	2.559 (1.215 – 5.392)	0.013	2.490 (1.180 – 5.256)	0.017	4.860 (1.664 – 14.195)	0.004	4.985 (1.705 – 14.576)	0.003	-	-	-	-
HADS-D	3.364 (1.513 – 7.479)	0.003	3.259 (1.462 – 7.263)	0.004	-	-	-	-	3.900 (1.280 – 11.885)	0.017	4.011 (1.315 – 12.241)	0.015

Abbreviations; HNSCC, head and neck squamous cell carcinoma; OR, Odds ratio; CI, Confidence interval; HADS-A, Hospital Anxiety and Depression Scale-Anxiety; HADS-D, Hospital Anxiety and Depression Scale-Depression.

[a]These variables remained in the final regression model.

[b]Values were adjusted for sex, age, marital status, comorbidity, tobacco and alcohol consumption, use of medications that affect sleep and BMI.

All values are considered statistically significant at $p<0.05$

4 DISCUSSION

Sleep disturbances are prevalent in HNSCC patients before, during and after treatment [37] and have a close relationship with their reduced quality of life [55]. In the current study, we investigated the influencing factors for pretreatment sleep quality and disorders in HNSCC patients exploring demographic, clinicopathological, and psychological variables. Herein, we demonstrated that 49.6% of HNSCC patients have poor sleep quality. Furthermore, our results reveal for the first time that pain, anxiety and depression symptoms measured prior to cancer treatment affect the HNSCC patients' sleep pattern. HNSCC patients with pain had a 6.4-fold increase in the chance of having poor sleep quality. Tumor-related pain and sleep disorders are often reported by HNSCC patients [34,56]. However, only one study has investigated the effects of pain on sleep quality prior to oncology treatment in this population. Santoso et al. [34] revealed that higher pain intensity was a risk factor of poor sleep quality in patients HNSCC. Despite showing a significant association between pain intensity and sleep quality in a large cohort of patients, this study showed that increased pain intensity led to a slight increase in the patient's risk exhibit poor sleep quality. Furthermore, this study did not assess whether the occurrence of pain, regardless of its intensity, could affect sleep quality. In the current study, regression analyses showed that, together with elevated levels of anxiety symptoms, pain derived from the head and neck tumors was highly associated with the poor sleep quality in HNSCC patients. Moreover, we showed that poor sleep quality also influenced the tumor-related pain. In this context, previous studies have shown that poor sleep quality can intensify the patient's perception of pain [57-58]. Lung cancer patients with insomnia, for example, report higher levels of pain and lower quality of life than those non-insomnia individuals [57]. Another study revealed that cancer patients with sleep disorders had a greater pain level than patients without sleep-related disturbances [59]. These findings, together with ours, reinforce the importance of tumor-related pain management to reduce sleep disorders and vice versa in cancer patients.

In this study, HNSCC patients with increased anxiety symptoms measured by HADS-A were 5.8 times more likely to have poor sleep quality before cancer treatment. Other studies have also explored the relationship between anxiety and sleep in cancer patients before starting treatment [60-61]. For instance, higher levels of anxiety symptoms together to female sex and be in a closed ward environment were risk factors of worse sleep quality in a cluster of patients with different types of cancer [60]. In HNSCC patients, Zhou et al. [61] demonstrated that individuals who felt "low-anxious" displayed fewer sleep problems than those who felt "high-

anxious". Nevertheless, Zhou et al. measured anxiety levels based on a single question of the 53-item You, Your Family, and the City of Hope are a Team instrument. Likewise, assessment of sleep problems was also based on a single question from the aforementioned instrument. In our study, HNSCC patients with increased levels of anxiety took more than 30 minutes to fall asleep (higher sleep latency), had reduced sleep efficiency, greater intensity of daytime dysfunction and symptoms of insomnia before starting treatment. To our knowledge, no study has demonstrated similar results. Although the effect of anxiety symptoms on sleep latency was lost after adjustment for BMI, reduced efficiency and daytime dysfunction may indicate insomnia linked to HPA axis hyperactivity among highly anxious patients. Anxiety is commonly accompanied by neuroendocrine changes, resulting in increased levels of stress-related hormones such as cortisol, norepinephrine and epinephrine [24,25,62]. Recently, a study by our team showed that pain, alcohol consumption and the emotional symptom "feeling of fear of losing control" were independent predictors of systemic cortisol concentrations in OSCC patients [26]. The hypersecretion of stress hormones leads to a state of permanent arousal, which in turn may affect sleep quality [63]. In this context, Chang et al. [28] revealed that flatter cortisol slope was a significant predictor of poor sleep quality in patients with newly diagnosed lung cancer. Another study demonstrated a positive correlation between cortisol concentrations and higher incidence of insomnia symptoms, especially the symptom "difficulty falling asleep", and daytime sleepiness in breast cancer survivors [64]. In a previous study we did not find associations between the levels of the catecholamines norepinephrine and epinephrine and sleep quality self-reported by HNSCC patients [65]. However, unlike what was carried out in this investigation, in that study we did not use structured questionnaires to evaluate sleep quality. Even so, we revealed that sleep deprivation and worse sleep quality were risk factors for higher systemic norepinephrine levels in patients with oral leukoplakia [65], a potentially malignant disorder that may precede the development of squamous cell carcinoma in oral cavity. Although we did not evaluate the stress hormone levels in our HNSCC patients' sample, we suggest that stress and anxiety related to the presence of the tumor, knowledge of the diagnosis, and expectation for treatment or a combination of these factors may lead to HPA axis hyperactivation, resulting in worse sleep quality and increase in insomnia symptoms. Furthermore, research has shown that smoking and alcoholism can modulate sleep quality. Current smokers display shorter sleep duration and increased sleep latency [66,67]. Similarly, alcoholism is associated with worse sleep quality, shorter sleep duration and snoring in general population [68]. In our sample, 67% of patients were smokers while 49% were drinkers at the time of diagnosis. Although tobacco and alcohol consumption were not predictive of sleep

quality in HNSCC patients, we cannot rule out that smoking and alcoholism could affect psychological symptoms such as stress and anxiety, and act as an indirect mediator of sleep quality. In the current study, we also showed that poor sleep quality and sleep disorders predict higher levels of anxiety and depression symptoms, reinforcing that there is a two-way relationship between sleep and psychological distress.

Usually, anxiety symptoms occur simultaneously with depression symptoms in cancer patients [69,70]. The results of the current investigation showed that HNSCC patients with higher levels of depression symptoms were about 3 times more likely to display increased sleep latency and shorter sleep duration than those patients with lower levels of depression. No previous study has identified depression as predictor of sleep latency in cancer patients. Nevertheless, Palesh et al. [71] found that higher levels of depression were influencing factors of lower sleep duration in women with metastatic breast cancer. Depression also predicted problems with waking up during the night and daytime sleepiness [71]. However, Palesh et al. [71] did not define the time of diagnosis and/or treatment of the patients included in the research. Differently from our study, the authors assessed sleep using the Sleep Questionnaire, a 6-item version of the 27-item Structured Insomnia Interview and measured the depression with Center for Epidemiologic Studies Depression Scale. These factors make it difficult to compare both studies. The relationship between depression and sleep quality has been explored in other investigations. Miaskowski et al. [72] revealed that higher levels of anxiety and depression were predictors of increased levels of sleep disturbances in prostate cancer patients. Depression was also an influencing of poor sleep quality in HNSCC patients one year after cancer diagnosis [35]. In our study, depressive symptoms were predictors of frequent use of sleep-inducing medication and occurrence of excessive daytime sleepiness in HNSCC patients. The main sleep-inducing drugs used by general population and cancer patients are those gamma-aminobutyric acid (GABA) receptor agonists, such as benzodiazepines and Z-drugs including clonazepam, diazepam and zolpidem [73,74]. The activation of GABA receptors promotes hypnotic and anxiolytic effects and regulates the stress response [74,75]. Therefore, impaired GABAergic signaling is directly associated with an imbalance of stress hormones release and sleep-related problems [74]. No research demonstrated that depression leads to increased consumption of sleep-inducing medications in cancer patients before treatment. Therefore, we suggest that HNSCC patients can show a dysfunction in GABAergic signaling, which results in the stress-related axis activation and release of cortisol and catecholamines. Stress hormones, in turn, may stimulate brain areas and promote psychological symptoms and poor sleep quality followed by higher use of sleep medication. Additionally, it is plausible to

think that HNSCC patients who were not encouraged to recognize and manage their psychological vulnerability prefer to take hypnotic medications as “an escape route” to avoid emotional distress caused by cancer diagnosis. Further investigations should be carried out to confirm these relationships in HNSCC patients and other types of cancer.

Studies have suggested a close relationship between sleep disorders and cancer onset, progression, and recurrence [8,9]. In this sense, a prospective cohort study showed that worst sleep quality was linked to increased risk of overall cancer and individuals with insomnia and snoring status displayed higher chance of developing different types of cancer, including HNSCC [76]. Sleep disorders, such as insomnia and short sleep duration have been associated with worse survival outcomes in both general population and cancer patients [77,78]. Furthermore, Jacob et al. [79] revealed that sleep disturbances were associated with an increase in the occurrence of metastases in breast cancer women after 5 years of follow-up. Surprisingly, the results of the current study showed that occurrence of regional metastasis was predictive of good sleep quality in HNSCC patients, according to the overall PSQI score. We believe that this result may have been influenced by patient self-report of “subjective sleep quality” and “sleep duration”. Here, 81% of patients with regional metastasis classified their sleep as being “very good” or “good” while 73% of them reported sleeping more than 7 hours per night. Then, we suggest some hypotheses. First, patients with advanced stage cancer display elevated levels of fatigue and drowsiness [80,81]. Cancer-related fatigue results in functional disability, feeling of tiredness, exhaustion or lack of energy [20] which could lead to increased somnolence and resulting in greater sleep duration. A descriptive study revealed that more than 80% of patients with advanced cancer submitted to palliative treatment displayed hypersomnolence [82]. Second, in this study, the occurrence of regional metastasis was associated with the use of analgesics. The better sleep quality observed in patients with regional metastasis could be associated with the use of analgesic, including opioid medications to treat pain caused by the tumor. It is knowledge that these drugs promote somnolence, feeling of well-being and relieves anxiety [83].

Despite demonstrating relevant results for understanding the factors influencing sleep quality in HNSCC patients, our study had some limitations. Sleep quality and disorders were evaluated based on the patients' perception. First, it was not possible to objectively measure sleep quality of HNSCC patients, using polysomnography or actigraphy to know the frequency and duration of REM and non-REM sleep episodes and occurrence of circadian rhythm disorders. Second, we did not evaluate the occurrence of cancer-related fatigue, which could influence daytime sleepiness and sleep quality in our sample. Furthermore, the anxiety and

depression symptoms were assessed by the HADS and not by a standardized psychiatric evaluation. Finally, the assessment of sleep quality in patients with HNSCC was performed only at one time point, so that the trajectory of changes in sleep patterns throughout cancer treatment and follow-up, as well as their impact on clinical outcomes, were not explored. Even so, our results reveal that primary tumor-related pain and higher levels of anxiety and depression symptoms are predictive of poor sleep quality in HNSCC patients. Furthermore, anxiety symptoms also affected sleep latency, efficiency and daytime dysfunction. Depressive symptoms in turn negatively impacted sleep latency and duration in HNSCC patients before starting treatment. Our findings indicate that psychological or pharmacological interventions to management of pain and emotional symptoms can be beneficial for improving sleep quality and well-being in HNSCC patients.

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ANEXOS

ANEXO A – Comissão de Ética em Pesquisa

UNESP - FACULDADE DE ODONTOLOGIA-CAMPUS DE ARAÇATUBA/ UNIVERSIDADE ESTADUAL PAULISTA "JÚLIO DE MESQUITA FILHO"

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Distúrbios do sono e alterações do sistema melatonérgico em pacientes com câncer de cabeça e pescoço: análise dos fatores preditores e prognóstico

Pesquisador: GISELI MITSUY KAYAHARA

Área Temática:

Versão: 1

CAAE: 52975221.6.0000.5420

Instituição Proponente: Faculdade de Odontologia do Campus de Araçatuba - UNESP

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 5.117.551

Apresentação do Projeto:

O estudo será constituído por 4 grupos experimentais: 1) 150 pacientes com câncer de cabeça e pescoço; 2) 50 pacientes com leucoplasia; 3) 50 pacientes com líquen plano e 4) 50 indivíduos saudáveis. Os níveis de trauma na infância, ansiedade e depressão serão avaliados pelos questionários Childhood trauma Questionnaire e HADS, respectivamente. Para avaliação da presença de distúrbios do sono e níveis de qualidade de vida serão aplicados instrumentos padronizados e validados para a população brasileira. As concentrações de melatonina e seu metabólito 6-sulfatoximelatonina serão dosadas em amostras de saliva e urina por meio da técnica de ELISA. Actigrafia será utilizada para avaliar a ritimicidade circadiana dos pacientes incluídos no estudo e ressonância magnética será utilizada para análise morfológica da glândula pineal. A expressão tumoral dos receptores de melatonina (MT1 e MT2) e das enzimas responsáveis pela produção (AANAT e ASMT) e metabolização (CYP1B) da melatonina serão avaliadas por imunoistoquímica. Testes estatísticos específicos serão aplicados para avaliar diferenças significantes entre os grupos.

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Continuação do Parecer: 5.117.551

Projeto Detalhado / Brochura Investigador	Projeto_de_Pesquisa_Giseli_Mitsuy_Kayahara.pdf	28/10/2021 16:53:34	GISELI MITSUY KAYAHARA	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

ARACATUBA, 22 de Novembro de 2021

Assinado por:
Aldiéris Alves Pesqueira
(Coordenador(a))

ANEXO B – Periódico para submissão

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