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ORIGINAL ARTICLE

Assessment of sleep disturbance in oral lichen planus and validation of PSQI: A case-control multicenter study from the SIPMO (Italian Society of Oral Pathology and Medicine)

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Abstract

Background: The wellbeing of oral lichen planus patients (OLPs) may be strongly influenced by a poor quality of sleep (QoS) and psychological impairment. The aims were to analyze the prevalence of sleep disturbance, anxiety, and depression in OLPs and to validate the Pittsburgh Sleep Quality Index (PSQI) in OLPs.

Methods: Three hundred keratotic OLPs (K-OLPs), 300 with predominant non-keratotic OLP (nK-OLPs), and 300 controls were recruited in 15 Italian universities. The PSQI, Epworth Sleepiness Scale (ESS), Hamilton Rating Scales for Depression and Anxiety (HAM-D and HAM-A), Numeric Rating Scale (NRS), and Total Pain Rating Index (T-PRI) were administered.

Results: Oral lichen planus patients had statistically higher scores than the controls in the majority of the PSQI sub-items (p-values $< 0.001^{**}$). Moreover, OLPs had higher scores in the HAM-D, HAM-A, NRS, and T-PRI (p-values $< 0.001^{**}$). No differences in the PSQI sub-items' scores were found between the K-OLPs and nK-OLPs, although nK-OLPs suffered from higher levels of anxiety, depression, and pain (p-values: HAM-A, 0.007^{**}, HAM-D, 0.009^{**}, NRS, $<0.001^{**}$, T-PRI, $<0.001^{**}$). The female gender, anxiety, depression (p-value: 0.007^{**}, 0.001^{**}, 0.020^{*}) and the intensity of pain, anxiety, and depression (p-value: 0.006^{**}, $<0.001^{**}$, 0.014^{*}) were independent predictors of poor sleep (PSQI > 5) in K-OLPs and nK-OLPs, respectively. The PSQI's validation demonstrated good internal consistency and reliability of both the total and subscale of the PSQI.

Conclusions: The OLPs reported an overall impaired QoS, which seemed to be an independent parameter according to the regression analysis. Hence, clinicians should assess QoS in OLPs and treat sleep disturbances in order to improve OLPs management.

KEYWORDS
anxiety, insomnia, mood disturbance, oral lichen planus, sleep disturbance

1 | INTRODUCTION

Oral lichen planus (OLP) is an immune-mediated inflammatory disease of the oral mucosa characterized by a chronic condition.[1] It may appear with different clinical patterns ranging from keratotic manifestations (K-OLP, white reticular, papular, and/or plaque-like lesions), generally asymptomatic, to predominantly non-keratotic lesions (nK-OLP, atrophic, erythematous, erosive, ulcerative, and/or bullous lesions),[2] which may be symptomatic and impair quality of sleep (QoS), mood, and subsequently the quality of life of the affected patients.

The occurrence of two most common sleep disturbances (SDs), insomnia, and daytime sleepiness, with or without mood disorders such as anxiety and depression, has been previously reported in OLP patients (OLPs).[3] However, only a few single center studies have investigated QoS,[4,5] this research based on limited samples, and no data are available in relation to the OLPs with different clinical patterns. Therefore, we aimed to perform a multicenter study in order to further analyze QoS, in a large cohort of OLPs analyzing differences between K-OLP and nK-OLP patterns. Moreover, to the best of our knowledge, this is the first study, which has assessed QoS in such a wide number of OLPs.

The objectives of the present study were as follows:

- to analyze the prevalence of insomnia and daytime sleepiness and their association with anxiety and depression in patients with keratotic OLP (K-OLPs) and patients with predominant non-keratotic OLP (nK-OLPs), in comparison with a control group of healthy subjects;
- to investigate the correlation between poor sleep, anxiety and depression with the oral symptomatology of K-OLP and nK-OLP;
- to validate the use of the Pittsburgh Sleep Quality Index (PSQI) in the screening of insomnia in OLPs.

2 | METHODS

2.1 | Participants

An observational multicenter case-control study was carried out between December 2018 and January 2020, in accordance with the ethical principles of the World Medical Association Declaration of

Helsinki and the methods conformed to the STROBE checklist and the statement for observational studies.[6] The Ethics Committee of the Federico II University of Naples approved the study (reference number: 184/18) and all the fifteen Italian Oral Medicine outpatients' departments joined with the Italian Society of Oral Pathology and Medicine (SIPMO—Società Italiana di Patologia e Medicina Orale) in participating in the research, having obtained the appropriate ethical approval from their local ethics committee.

All potentially eligible participants of either gender, aged >18 and willing to participate provided their written informed consent. The patients and controls were matched by age and gender (Appendix -Methods).

In the K-OLP and nK-OLP groups, patients with clinical and histopathological findings of OLP based upon the modified WHO diagnostic criteria[7] were included. Moreover, patients with an exclusive presence of white reticular, papular, and/or plaque-like lesions (the keratotic pattern) were selected for the K-OLP-group while patients with prevalent erythematous, ulcerative and/or bullous patterns (the predominant non-keratotic pattern) were selected for the nK-OLP group.

Conversely, patients with evidence of oral epithelial dysplasia, oral lesions potentially related to any drug use or oral restorations, or any other identified oral mucosal disease, or OLP cutaneous lesions were excluded from both groups.

In the control group, we included participants referred to the dental clinics of the same universities for routine dental care during the study period without any history of an oral mucosal disease.

In all three groups, pregnant or breastfeeding women, patients with serious systemic diseases, for instance oncological diseases such as solid tumors (breast, prostate, kidney, lung cancers, etc.) or hematological malignant disease (leukemia, multiple myeloma, etc.), severe neurological disorders (Alzheimer disease, Dementia, Multiple Sclerosis), autoimmune diseases (Rheumatoid Arthritis, Systemic Lupus Erythematous, Systemic Sclerosis), history, or occurrence of psychiatric illness, as defined by the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders V (DSM-V), or a history of alcohol or substance abuse, patients undergoing treatment with systemic and/or topical corticosteroids or psychotropic drugs, and individuals unable to understand the questionnaires were excluded.

2.2 | Measures

The clinical assessment of all the participants is reported in detail in the Appendix -Methods.

Any SDs were identified and diagnosed based on the DSM-V criteria (Appendix -Methods). The OLPs and healthy subjects were assessed with the following predefined set of questionnaires:

- the PSQI and the Epworth Sleepiness Scale (ESS) for the assessment of SDs.[8,9]
- the Hamilton Rating Scale for Depression (HAM-D) and the Hamilton Rating Scale for Anxiety (HAM-A) for the evaluation of depression and anxiety.[10,11]
- the Numeric Rating Scale (NRS) and Total Pain Rating Index (T-PRI) from the Short Form of the McGill Pain Questionnaire (SF-MPQ) for the assessment of oral discomfort and the intensity and quality of pain.[12,13]

All these scales were reviewed for completeness before collection and were administered in their Italian versions (Appendix -Methods).

2.3 | Statistical analysis

The total sample size, equal to 300 patients for each of the three groups, was calculated to obtain a test power of no less than 90% associated with a significance of no more than 5%. This evaluation was obtained by considering the results of a previous research[4] from which an estimate of the effect size (Cohen's d) equal to 0.225 was obtained in relation to the mood disorders scales. The calculations were carried out with the GPower software.

The statistical analysis was performed using the SPSS software V. 23. Descriptive statistics were used to analyze the sociodemographic and clinical characteristics of the three groups. Pearson's chi-squared test was used to test the significance differences between the percentages in the three groups. Differences associated with p-values < 0.05 or 0.01 were considered moderately or strongly significant, respectively. The non-parametric ANOVA procedure by Kruskal-Wallis was employed to test for any differences between the recorded medians of the PSQI, ESS, HAM-D, HAM-A, NRS, and T-PRI of the groups. p-values < .05 were considered to reflect a statistical significance. Pearson's chi-squared was used to analyze the frequency differences of the oral symptoms and oral sites in K-OLPs and nK-OLPs poor sleepers and good sleepers. Multiple linear regression analysis was performed to test the importance of the effect of the disease-related and psychological factors to QoS after checking for demographic factors. A full model, when all the variables were entered simultaneously into the model, was used to evaluate the relative contributions of these variables to QoS.

3 | RESULTS

A total of 300 K-OLPs, 300 nK-OLPs and 300 controls were enrolled with no missing data recorded. Table 1 shows the sociodemographic characteristics, health related factors, comorbidities, and drug consumption of the patients and controls.

The entire PSQI validation process is provided in the Appendix-Results (Table 1A–C). A Cronbach's alpha value of 0.75 was calculated, showing a good overall internal consistency and reliability of the test.

In order to remove the co-founding effects of significant sociodemographic characteristics (Table 1), a statistical matching approach[14] based on nearest neighbor distance, has been applied before comparing sleep quality, anxiety, depression scores between patients and controls. As shown in Table 2, a statistically significant higher proportion of OLPs were poor sleepers (PSQI > 5),

TABLE 1 Sociodemographic profile and health related factors in the 300 K-OLP patients, 300 nK-OLP patients, and 300 controls

	K-OLPs	nK-OLPs	Controls	
Demographic variables	**N°/ Frequency (%)**	**N°/ Frequency (%)**	**N°/ Frequency (%)**	***p*-Value**
Gender				
Male	125 (41.7)	125 (41.7)	125 (41.7)	1.000
Female	175 (58.3)	175 (58.3)	175 (58.3)	
Employment				
Employed	108 (36.0)	80 (26.7)	155 (51.7)	<0.001**
Unemployed	113 (37.7)	158 (52.7)	68 (22.7)	
Retired	79 (26.3)	62 (20.7)	77 (25.7)	
Family situation				
Single	37 (12.3)	27 (9.0)	82 (27.3)	<0.001**
Married	217 (72.3)	209 (69.7)	176 (58.7)	
Divorced	16 (5.3)	14 (4.7)	24 (8.0)	
Widowed	30 (10.0)	50 (16.7)	18 (6.0)	
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	
Age (in years)	65.2 ± 12.2	64.6 ± 12.6	64.2 ± 16.9	0.686
Education (in years)	10.9 ± 4.0	11.0 ± 4.4	13.6 ± 4.5	<0.001**
Body Mass Index	24.9 ± 3.9	25.0 ± 4.0	24.3 ± 3.6	0.041*
Disease onset (in years)	4.5 ± 2.3	4.3 ± 2.7	NA	0.020*
Risk factors	**N°/ Frequency (%)**	**N°/ Frequency (%)**	**N°/ Frequency (%)**	
Smoking				
Yes	66 (22.0)	52 (17.3)	96 (32.0)	<0.001**
No	234 (78.0)	248 (82.7)	204 (68.0)	
Alcohol consumption				
Yes (≤ 14 units/week)	91 (30.3)	83 (27.7)	95 (31.7)	0.552
No	209 (69.7)	217 (72.3)	205 (68.3)	
	K-OLPs	**nK-OLPs**	**Controls**	
Systemic diseases	**Frequency (%)**	**Frequency (%)**	**Frequency (%)**	***p*-Value**
Essential Hypertension	32.7	48.0	26.0	<0.001**
Hypercholesterolemia	22.3	23.0	16.7	0.109
Previous myocardial infarction	2.0	2.3	2.7	0.864
Diabetes	8.3	9.3	7.0	0.762
Asthma	2.3	5.7	2.3	0.035*
Gastro-esophageal reflux disease	15.3	21.3	9.0	<0.001**
Hepatitis B	1.3	0.7	0.0	0.134
Hepatitis C	3.3	3.3	1.3	0.214
Endocrine disease	3.7	5.3	2.0	0.094
Hypothyroidism	11.3	10.7	7.0	0.154
Hyperthyroidism	1.7	3.7	1.3	0.111
Benign prostatic hypertrophy	7.0	6.0	2.75	0.044*
Previous malignant disease	8.0	8.0	5.3	0.341
Drug Consumption				
Beta-Adrenergic receptor blockers	15.7	19.3	11.7	0.001**
Angiotensin II receptor blockers	8.0	8.3	5.7	0.394
Diuretics	8.0	8.3	8.0	0.985

(Continues)

TABLE 1 (Continued)

Systemic diseases	K-OLPs Frequency (%)	nK-OLPs Frequency (%)	Controls Frequency (%)	*p*-Value
Calcium Channel blockers	4.7	9.3	3.7	0.006**
ACE-inhibitors	9.3	19.7	10.3	<0.001**
Simvastatin	14.3	19.3	13.7	0.115
Metformin	8.0	6.7	5.3	0.424
Insulin	2.7	2.7	2.0	0.830
Antiplatelets	11.7	16.0	8.0	0.010**
Blood thinners	5.0	4.7	2.0	0.114
Levothyroxine sodium	12.0	12.0	6.3	0.029*
Proton pump inhibitors	14.0	19.7	11.7	<0.001*

Note: The significance difference among the medians was measured by the Kruskal-Wallis test. *Significant $0.01 < p \leq 0.05$, **Significant $p \leq 0.01$. The significance difference among the percentages was measured by the Pearson Chi Square test. *Significant $0.01 < p \leq 0.05$, **Significant $p \leq 0.01$. Abbreviations: keratotic oral lichen planus; K-OLP: nK-OLP: non-keratotic oral lichen planus.

TABLE 2 Frequency of insomnia, daytime sleepiness, depression and anxiety; total score analysis of the PSQI, ESS, HAM-D, HAM-A, NRS and T-PRI and comparison of components of PSQI, in K-OLP, nK-OLP patients and controls

Psychological Profile	K-OLPs N°/ Frequency (%)	nK-OLPs N°/ Frequency (%)	Controls N°/ Frequency (%)	*p*-Value
Sleep disturbance (PSQI ≥ 5)	138 (49.1)	145 (51.1)	109 (23.9)	0.002**
Daytime sleepiness (ESS ≥ 10)	37 (13.2)	60 (21.1)	52 (10.1)	0.115
Depression (HAM-D ≥ 7)	122 (43.4)	148 (52.1)	83 (17.2)	<0.001**
Anxiety (HAM-A ≥ 7)	131 (46.6)	152 (53.5)	94 (20.0)	<0.001**
Total score of tests	**K-OLPs Median; IQR**	**nK-OLPs Median; IQR**	**Controls Median; IQR**	***p*-Value**
PSQI	5.0; [3 – 8]	6.0; [4 – 9]	5.0; [3 – 7]	<0.001**
ESS	4.0; [2–7]	5.0; [2–8.25]	5.0; [2–8]	0.185
HAM-D	6.0; [3–12]	8.0; [4–13]	5.0; [2–9]	<0.001**
HAM-A	7.0; [3–12]	8.0; [4–15]	4.0; [2–10]	<0.001**
NRS	2.0; [0–5]	4.5; [1–7]	0.0; [0–0]	<0.001**
T-PRI	2.0; [0–5]	3.0; [1–7]	0.0; [0–0]	<0.001**
PSQI items				
Subjective sleep quality	1.0; [1 – 2]	1.0; [0 – 1]	1.0; [0 – 1]	0.017*
Sleep latency	1.0; [0 – 2]	1.0; [0 – 2]	1.0; [0 – 1]	0.054
Sleep duration	1.0; [1 – 2]	1.0; [1 – 2]	1.0; [0 – 1]	0.011*
Habitual sleep efficiency	1.0; [0 – 1]	0.0; [0 – 1]	0.0; [0 – 1]	0.006**
Sleep disturbances	1.0; [1 – 2]	1.0; [0 – 1]	1.0; [0 – 1]	<0.001**
Use of sleep medication	0.0; [0 – 1]	0.0; [0 – 1]	0.0; [0 – 0]	0.004**
Daytime dysfunction	0.0; [0 – 1]	0.0; [0 – 1]	0.0; [0 – 1]	0.123

Note: The significance difference among the medians was measured by the Kruskal-Wallis test. *Significant $0.01 < p \leq 0.05$, **Significant $p \leq 0.01$. The significance difference among the percentages was measured by the Pearson Chi Square test. *Significant $0.01 < p \leq 0.05$, **Significant $p \leq 0.01$. Abbreviations: ESS, Epworth sleepiness scale; HAM-A, Hamilton anxiety; HAM-D, Hamilton depression; K-OLP, keratotic oral lichen planus; nK-OLP, non-keratotic oral lichen planus; PSQI, Pittsburgh sleep quality index.

experiencing depression and anxiety (*p*-value: 0.002**, <0.001**, and <0.001**, respectively) compared to the controls. Indeed, the OLPs presented significantly higher medians of the PSQI, HAM-D, HAM-A, NRS, and T-PRI scores (*p*-values: <0.001**), while no differences were detected with respect to the frequency or median score of the ESS (*p*-values: 0.115 and 0.185, respectively). Specifically, the

analysis of the PSQI sub-item scores revealed a statistically significant difference between the OLPs and controls in the majority of the sub-items, namely subjective sleep quality, sleep duration, habitual sleep efficiency, sleep disturbances, and the use of sleeping medication (*p*-values: 0.017, 0.011, 0.006, <0.001 and 0.004, respectively), while no differences in the scores of the sleep latency and daytime dysfunction sub-items were found (*p*-values: 0.054 and 0.123, respectively).

Overall, the prevalence of poor sleep (PSQI ≥ 5) was higher in females, considering the median age of the sample. However, a relatively high frequency of poor QoS was detected also in younger male patients (20–39) (Appendix -Figure 1).

As reported in Appendix -Table 2A, despite no difference being found in terms of the frequency distribution of insomnia, depression, and anxiety between the nK-OLPs and K-OLPs (*p*-values: 0.514, 0.213, 0.165 and 0.102, respectively), the former presented statistically significant higher median scores for the HAM-D, HAM-A, NRS, and T-PRI in comparison with the K-OLPs (*p*-values: 0.007**, 0.009**, <0.001** and <0.001**, respectively). There was no difference in the median scores of the PSQI and ESS between the two groups. Overall, while anxiety and depression were more prevalent among the nK-OLP patients, QoS was similarly impaired in both groups. Indeed, the K-OLPs presented higher scores only in the PSQI sub-item sleep disturbances (*p*-value: 0.013) compared to the nK-OLPs.

A comparison of the psychological profiles between the K-OLPs and nK-OLPs sub-groups of good sleepers and poor sleepers showed that the nK-OLP good sleepers presented statistically significantly higher scores for the HAM-D, NRS and T-PRI (*p*-values: 0.030*, <0.001**, and <0.001**, respectively) compared with the K-OLP good sleepers. The nK-OLP poor sleepers reported higher median scores in all the variables (HAM-D, *p*-value: 0.034*; HAM-A, *p*-value: 0.004**; NRS, *p*-value: 0.001**; and T-PRI, *p*-value: 0.003**) except for the ESS (*p*-value: 0.176). Moreover, moderate-to-severe depression was more prevalent in the nK-OLPs (*p*-value: 0.032) in comparison to the K-OLPs. In addition, the majority of the K-OLP and nK-OLP good sleepers did not suffer from depression and anxiety (62% and 55.8%, respectively) while the majority of the K-OLP and nK-OLP poor sleepers were anxious and depressed (54.4% and 61.9%, respectively) (Table 3).

Table 4 shows differences on oral symptomatology between OLPs good and poor sleepers. Notably, the nk-OLP good sleepers reported statistically significantly higher percentages of pain/burning and sialorrhea than the K-OLP good sleepers (*p*-values 0.001 and 0.044, respectively). Similarly, the nK-OLP poor sleepers reported higher scores compared to the K-OLP poor sleepers (*p*-values: <0.001 and 0.030, respectively).

The results of the logistic regression analyses for the K-OLP and nK-OLP groups, predicting insomnia (PSQI > 5), are shown in Table 5 and the details are presented in the Appendix-Results. The final full model of the multivariate analysis (model 6), after controlling all of the variables, demonstrates the presence of four independent predictors of poor sleep (PSQI > 5) in the K-OLPs: female gender (F, OR: 2.26; *p*-value 0.007**), anxiety (HAM-A; OR:1.11, *p*-value: 0.001**), depression (HAM-D; OR: 1.08; *p*-value 0.020*), and intensity of pain (NRS; OR: 1.20, *p*-value: 0.006**). Moreover, two independent predictors were found in the nK-OLPs: anxiety (HAM-A; OR:1.14, *p*-value: <0.001**) and depression (HAM-D; OR: 1.09, *p*-value: 0.014*). Overall, the full model can explain 16.8% and 24.2%, of the variance of the poor sleep for the K-OLPs and nK-OLPs, respectively.

4 | DISCUSSION

This multicenter study has examined the prevalence of SDs, namely insomnia, daytime sleepiness, anxiety, and depression, in a representative cohort of 600 OLPs by analyzing for the first time the differences between patients with the K-OLP and nK-OLP subtypes. A particular strength of this study is the sample size, which is notably larger than previous studies on SDs and mood disorders in OLPs. In addition, we have tested the use of the PSQI as an adequate instrument for the evaluation of insomnia in OLPs.

The overall prevalence of poor sleep in our OLP sample was 50.3%. Specifically, 49% of the K-OLPs and 52% of the nK-OLPs were poor sleepers with a statistically significant difference in relation to the control group (*p* value: 0.002**). Moreover, the prevalence of daytime sleepiness in the OLPs was 17.8%, with a higher prevalence in the nK-OLPs (21.7%) compared with the K-OLPs (14.7%), but without any difference in relation to the healthy subjects (*p*-value: 0.115). In addition, each patient with PSQI > 5 met all the DSM-V's criteria with regard to insomnia diagnosis.

In this sample, a significant difference in five out of seven subscale scores of the PSQI has been found, suggesting that OLPs suffer from a worse subjective sleep quality and habitual sleep efficacy, a shorter sleep duration with a higher prevalence of SDs and a greater use of sleep medication (even if, in the inclusion criteria of the study, we considered only subjects reporting an occasional use of such drugs) compared with the controls. Instead, among the K-OLPs and nK-OLPs the former group of patients reported higher scores only in the item relating to sleep disturbances (*p*-value: 0.013*).

Our results revealed that female OLPs older than 50 years are more significantly affected by SDs than males, in line with the prevalence of poor sleep that is reported to be higher in people aged >65 years, especially females.[15] Nevertheless, and surprisingly, in our population SDs were also more prevalent in younger male patients (age: 20–39) compared to the female population of the same age.[16]

The prevalence of depression and anxiety was found in 48% and 51% of OLPs, respectively, with higher levels compared with the controls. Particularly, the nK-OLPs showed a higher prevalence of depression and anxiety compared with the K-OLPs, with a higher total score in the HAM-D and HAM-A scales but not in the PSQI and ESS scales. The majority of good sleepers in the K-OLP and nK-OLP groups were not depressed or anxious (62% and 55.8%, respectively). Instead, in line with the current literature where individuals with a poor QoS reported increased levels of mood disorders,

TABLE 3 Clinical characteristics and comparison between good sleepers and poor sleepers in the K-OLP and nK-OLP patients

	K-OLP Good sleepers PSQI < 5 (51.0%)	nK-OLP Good sleepers PSQI < 5 48.3%)		K-OLP Poor sleepers PSQI ≥ 5 (49.0%)	nK-OLP Poor sleepers PSQI ≥ 5 (51.7%)	
Clinical characteristics	**Median IQR range**	**Median IQR range**	***p*-Value**	**Median IQR range**	**Median IQR range**	***p*-Value**
Depression HAM-D	4; [1.5 – 8]	5; [3 – 8]	0.030*	9; [5 – 15]	11; [7 – 18]	0.034*
Anxiety HAM-A	4; [2 – 8]	4; [1 – 9]	0.258	10; [6 – 16]	14; [7.3 – 20]	0.004**
Daytime sleepiness ESS	3; [2 – 6]	4; [1.3 – 6]	0.831	6; [3 – 9]	7; [3 – 10]	0.176
Pain						
NRS	1; [0 – 3.5]	3; [0 – 5]	<0.001**	3; [0 – 6]	5; [2 – 7]	0.001**
T-PRI	1; [0 – 2]	2; [0 – 4]	<0.001**	3; [0 – 6]	5; [2 – 9]	0.003**
	N°/Frequency (%)	**N°/Frequency (%)**		**N°/Frequency (%)**	**N°/Frequency (%)**	
Depression						
0–7 (no)	129 (84.3)	118 (81.4)	0.760	74 (50.3)	64 (41.3)	0.032*
7–17 (mild)	18 (11.8)	23 (15.9)		49 (33.3)	50 (32.3)	
18–24(moderate)	5 (3.3)	3 (2.1)		18 (12.2)	30 (19.4)	
>24 (severe)	1 (0.7)	1 (0.7)		6 (4.1)	11 (7.1)	
Anxiety						
7–17 (mild)	139 (95.9)	148 (96.7)	0.712	108 (69.7)	116 (78.9)	0.093
18–24(moderate)	6 (4.1)	2 (1.3)		32 (20.6)	21 (14.3)	
>24 (severe)	0 (0.0)	3 (2.0)		15 (9.7)	10 (6.8)	
	K-OLP Good sleepers	**nK-OLP Good sleepers**		**K-OLP Poor sleepers**	**nK-OLP Poor sleepers**	
No D No A	95 (62)	81 (55.8)		35 (23.8)	26 (16.7)	
D No A	10 (6.5)	17 (11.7)		15 (10.2)	14 (9.0)	
No D A	19 (12.4)	20 (13.7)		17 (11.5)	19 (12.2)	
D A	29 (18.9)	27 (18.6)		80 (54.4)	96 (61.9)	

Note: The significance difference among the medians was measured by the Kruskal-Wallis test. *Significant $0.01 < p \leq 0.05$, **Significant $p \leq 0.01$.

The significance difference among the percentages was measured by the Pearson Chi Square test. *Significant $0.01 < p \leq 0.05$, **Significant $p \leq 0.01$.

Abbreviations: A, Anxiety; D, depression; ESS, Epworth sleepiness scale; HAM-A, Hamilton anxiety; HAM-D, Hamilton depression; K-OLP, keratotic oral lichen planus; nK-OLP, non-keratotic oral lichen planus; NRS, Numeric Rating Scale; PSQI, Pittsburgh sleep quality index; T-PRI, Total Pain Rating Index.

TABLE 4 Oral symptoms and oral sites involved in good sleepers and poor sleepers with K-OLP and nK-OLP

	K-OLP		nK-OLP					
	Good sleepers *n*°= 153 51%	Poor sleepers *n*°= 147 49%	Good sleepers *n*°= 145 48.3%	Poor sleepers *n*°= 155 51.7%	K-OLP good vs K-OLP poor sleepers	nK-OLP good vs nK-OLP poor sleepers	K-OLP good vs nK-OLP good sleepers	K-OLP poor vs nK-OLP poor sleepers
	Frequency (%)	Frequency (%)	Frequency (%)	Frequency (%)	*p*-Value	*p*-Value	*p*-Value	*p*-Value
Oral symptoms								
Pain/Burning	43.1	56.5	62.8	71.6	0.131	0.028*	0.001**	0.001**
Xerostomia	29.4	38.4	31.7	37.4	0.360	0.142	0.759	0.628
Dysgeusia	16.3	22.4	20.7	23.2	0.696	0.233	0.413	0.597
Sialorrhea	7.2	13.6	15.2	21.9	0.176	0.102	0.044*	0.030*
Subjective halitosis	17.0	19.7	17.9	22.6	0.392	0.644	0.952	0.343
Globus pharyngeus	9.8	17.0	9.0	24.5	0.001**	0.096	0.961	0.597
Itching	9.2	13.7	9.0	16.1	0.091	0.301	1.000	0.399
Intraoral foreign body sensation	6.5	17.0	9.0	16.1	0.091	0.008**	0.570	0.958
Tingling sensation	5.9	13.6	11.0	14.2	0.517	0.039**	0.163	0.723
Occlusal Dysesthesia	5.2	10.2	8.3	9.7	0.824	0.161	0.413	1.000
Change in tongue morphology	0.0	1.4	1.4	0.0	0.449	0.461	0.455	0.502
Oral dyskinesia	0.0	4.8	0.7	4.5	0.090	0.019*	0.979	1.000
Dysosmia	6.5	6.1	2.8	9.7	0.026*	1.000	0.205	0.229
Oral sites involved								
Gingiva	37.9	40.8	37.2	47.7	0.085	0.691	1.000	0.053
Lips	26.1	32.7	20.7	27.1	0.245	0.267	0.330	0.744
Buccal mucosa	42.8	49.0	36.6	55.5	0.002**	0.311	0.353	0.045*
Tongue	39.2	43.5	34.5	44.5	0.097	0.520	0.468	0.378
Floor of the mouth	19.6	25.9	11.8	18.7	0.129	0.249	0.088	0.389
Hard palate	28.8	31.3	21.4	29.0	0.164	0.724	0.182	0.956
`Soft palate	17.0	23.8	10.3	20.0	0.031*	0.186	0.134	0.864

Note: The significance difference among the percentages was measured by the Pearson Chi Square test. *Significant $0.01 < p \leq 0.05$, **Significant $p \leq 0.01$.

Abbreviations: K-OLP, keratotic oral lichen planus; nK-OLP, non-keratotic oral lichen planus.

TABLE 5 Logistic regression analysis predicting Poor Sleep (PSQI≥5) in the 300 K-OLPs and 300 nK-OLPs

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6	
K-OLP	**OR**	***p*-Value**	**OR**	***p*-Value**	**OR**	***p*-Value**	**OR**	***p*-Value**	**OR**	***p*-Value**	**OR**	***p*-Value**
Age	1.01	0.572	1.01	0.505	1.01	0.594	1.01	0.477	1.01	0.542	1.01	0.475
Gender: F	2.35	0.001**	2.42	0.003**	2.27	0.005**	2.13	0.005**	2.14	0.005**	2.26	0.007**
Years of education	1.02	0.652	1.04	0.342	1.02	0.590	1.01	0.682	1.02	0.650	1.03	0.436
Marital status: Married	0.94	0.820	1.00	0.990	1.11	0.732	0.95	0.850	0.97	0.928	1.05	0.886
Job: Occupied	0.98	0.919	1.03	0.792	0.94	0.681	0.99	0.731	1.01	0.689	1.03	0.671
Smoker	1.09	0.774	0.95	0.883	1.06	0.853	1.14	0.667	1.17	0.603	0.92	0.817
Alcohol	0.85	0.550	1.36	0.321	1.25	0.466	0.96	0.879	0.96	0.875	1.54	0.185
BMI	1.01	0.634	1.01	0.691	1.01	0.665	1.01	0.732	1.02	0.578	1.01	0.753
Disease onset	1.02	0.698	1.03	0.721	1.03	0.702	1.03	0.756	1.01	0.654	1.04	0.666
Anxiety (HAM-A)			1.16	<0.001**							1.11	0.001**
Depression (HAM-D)					1.15	<0.001**					1.08	0.020*
Intensity of pain (NRS)							1.17	<0.001**			1.20	0.006**
Quality of pain (T-PRI)									1.10	0.002**	0.92	0.086
R^2 (%)	3.6	0.051	17.0	<0.001**	14.9	<0.001**	6.8	0.001*	6.3	0.002	20.1	<0.001**
R^2*change* (%)			13.4	<0.001**	11.3	<0.001**	3.2	0.001**	2.7	0.002**	16.8	<0.001**
	Model 1		**Model 2**		**Model 3**		**Model 4**		**Model 5**			
nK-OLP	**OR**	***p*-Value**	**OR**	***p*-Value**	**OR**	***p*-Value**	**OR**	***p*-Value**	**OR**	***p*-Value**	**OR**	***p*-Value**
Age	1.01	0.941	1.01	0.368	1.00	0.727	1.00	0.892	1.00	0.687	1.01	0.450
Gender: F	1.30	0.336	1.50	0.196	1.70	0.076	1.23	0.442	1.18	0.545	1.53	0.185
Years of education	1.03	0.081	0.98	0.545	0.97	0.392	0.95	0.131	0.95	0.105	0.98	0.584
Marital status: Married	1.31	0.667	1.07	0.832	1.13	0.687	1.13	0.662	1.15	0.613	1.12	0.729
Job: Occupied	1.01	0.701	0.96	0.810	1.11	0.791	1.03	0.583	0.99	0.833	1.00	0.451
Smoker	1.40	0.109	1.49	0.322	1.71	0.168	1.76	0.101	1.73	0.110	1.65	0.223
Alcohol	1.32	0.172	1.08	0.822	1.02	0.944	0.64	0.127	0.57	0.057	1.05	0.892
BMI	1.03	0.827	0.98	0.546	1.02	0.594	1.00	0.991	1.01	0.858	1.00	0.924
Disease onset	1.01	0.566	1.04	0.785	1.02	0.528	0.98	0.435	1.01	0.558	1.01	0.653
Anxiety (HAM-A)			1.21	<0.001**							1.14	<0.001**
Depression (HAM-D)					1.21	<0.001**					1.09	0.014*
Intensity of pain (NRS)							1.16	0.003			0.99	0.891
Quality of pain (T-PRI)									1.10	<0.001**	1.03	0.273
R^2 (%)	2.8	0.133	24.7	<0.001**	21.1	<0.001**	6.3	0.002**	7.7	0.001**	27.0	<0.001**
R^2*change* (%)			21.9	<0.001**	18.3	<0.001**	3.5	0.003**	4.9	0.002**	24.2	<0.001**

Note: SE are the standard errors of the beta estimates. The *p*-values were obtained from the hypothesis test on the regression coefficients.

*Moderately significant.01 < *p*-value ≤ 0.05.

**Strongly significant *p*-value≤.01.

Abbreviations: BMI, Body Mass Index; HAM-A, Hamilton rating scale for anxiety; HAM-D, Hamilton rating scale for depression; K-OLP, keratotic oral lichen planus; nK-OLP, non-keratotic oral lichen planus; NRS, Numeric Pain Intensity Scale; PSQI, Pittsburgh sleep quality; T-PRI, Total Pain Rating Index.

a majority of both the K-OLP and nK-OLP poor sleepers were depressed and anxious (54.4% and 61.9%, respectively) with a higher frequency of moderate and severe depression in the nK-OLPs, suggesting that poor sleep may be considered a contributor to depression and anxiety.

Among the general population, alcohol consumption and a high BMI are recognized as risk factors that impact on sleep negatively.[17] However, in our study from the analysis of the logistic regression these two factors did not emerge as predictors of insomnia in the OLPs. Instead, female gender, anxiety, depression, and intensity of pain were predictors of poor sleep for the K-OLPs, with only anxiety and depression being predictors for the nK-OLPs. The mechanisms connecting mood disorders and poor sleep remain unclear, and just a few integrative theories have been proposed.[18] However, these data suggest a bidirectional relationship between mood disorders and poor sleep, despite many studies having suggested that insomnia may precede psychological impairment by many years.[19,20] This finding can be confirmed by the analysis of the last model of the hierarchical regression (model 6). Indeed, all the variables entered simultaneously can explain only 16.8% and 24.2% of the variance of poor sleep for the K-OLPs and nK-OLPs, respectively, suggesting that sleep impairment could be in many cases an independent parameter and may precede mood disorders.[21] A potential bidirectional relationship may also exist between poor sleep and pain since in this study intensity of pain was a predictor of poor sleep in patients with K-OLP, even though it is also known that the persistence of untreated poor sleep may in turn amplify pain perception over time,[22] especially in the clinical subtype of K-OLP, a condition which is generally asymptomatic.[4,23]

Until now, no specific tools have been validated for the evaluation of sleep quality in OLP. However, across the world the PSQI is the measure that is most frequently used in relation to many diseases.[24] The present study suggests that the PSQI is an appropriate qualitative and quantitative tool for the assessment of sleep in OLPs. The screening and treatment of insomnia, frequently undetected, in patients with OLP could be essential in terms of improving the care, prognosis, and quality of life of these patients.[5,25] The co-occurrence and persistence over the long term of insomnia, particularly in immune-related diseases such as OLP, may exacerbate not only the chronic course of the disease, contributing to the pain perception but may also affect the severity and course of any associated mood disorders.[19,20] Similarly, both factors could worsen further the QoS. Indeed, from the analysis of this study, both the K-OLP and nK-OLP poor sleepers show a higher frequency of oral pain/burning and additional oral symptoms compared with the good sleepers. In particular, the nK-OLP patients showed a higher frequency and intensity of pain.

The current study has demonstrated that, in the majority of cases, poor sleep can occur independently of the presence of any predictors. This finding could support the hypothesis that insomnia may be triggered by immunological mechanisms in which a dysregulated homeostatic cytokine expression has been identified. Indeed, a bidirectional communication between the central nervous system and immune system has been demonstrated.[25] Therefore, the increase of local pro-inflammatory cytokines, such as interleukin-1(IL-1), interleukin-6(IL-6), interleukin-8(IL-8), interleukin-10(IL-10), interleukin-17(IL-17), and tumor necrosis factor (TNF-α), can access the brain, contributing to the etiopathogenesis of SDs.[26–28] In turn, sleep loss increases further the level of these cytokines,[25] which can exacerbate OLP and contribute to the inflammation and the self-reported symptomatology.

In addition, Li et al.[29] have found a dysregulation of some metabolites in the serum of K-OLPs, which could further support the hypothesis that poor sleep is caused by the disease itself and is an independent parameter to identify. Indeed, in this study the oleamide level was significantly reduced in the serum of OLPs. Recently, it has been proposed that this lipid is involved in the regulation of several physiological functions and has a key role in inducing sleep.[30] In addition, a low plasma level of L-tryptophan, a precursor of serotonin (5-HT), has been found in patients with K-OLP.[31] Therefore, the authors of these studies have concluded that a low level of oleamide and L-tryptophan might directly induce poor sleep in OLP patients and indirectly negatively affect mood.[29] Further studies are needed to confirm our findings and to explore the underlying pathophysiological mechanisms of sleep, mood, and pain in OLP.

4.1 | Limitations

The results of the study should be considered exploratory and interpreted carefully, taking into account the cross-sectional design of the study and the fact that the analysis has been made in relation to tertiary referral Oral Medicine Units. Therefore, there may be confounding factors due to the heterogeneity of the case-control study, particularly in a multicenter setting. In addition, it is not possible to establish a cause-effect relationship between sleep, mood, and pain due the nature of the study design. Finally, our findings may not be relevant to different populations.

5 | CONCLUSIONS

Sleep disturbances continue to be undiagnosed and untreated in OLP, negatively affecting the quality of life of patients. The present study has confirmed the high prevalence of insomnia and mood disorders in OLPs, with nK-OLPs presenting a higher prevalence compared with K-OLPs. As approximately 50% of OLPs suffer from poor sleep, anxiety, and depression, it is crucial to assess the psychological status of all patients with this condition. The PSQI has proved to be a suitable tool useful for the evaluation of QoS in OLPs.

Although we have identified predictors for poor sleep, namely female gender, anxiety, depression and intensity of pain for K-OLPs and anxiety and depression for nK-OLPs, in the majority of OLP cases poor sleep was an independent parameter. The early recognition and management of insomnia could help clinicians to provide a better long-term care for OLPs by potentially avoiding the aggravation of

anxiety and depression and preventing the exacerbation of disease, thereby improving the quality of life of OLPs.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

AUTHOR CONTRIBUTION

Daniela Adamo: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Validation; Visualization; Writing-original draft; Writing-review & editing. **Elena Calabria:** Conceptualization; Data curation; Investigation; Methodology; Visualization; Writing-original draft; Writing-review & editing. **Noemi Coppola:** Data curation; Investigation; Methodology; Writing-review & editing. **Lorenzo Lo Muzio:** Data curation; Investigation; Writing-review & editing. **Michele Giuliani:** Data curation; Investigation; Writing-review & editing. **Lorenzo Azzi:** Data curation; Investigation; Writing-review & editing. **Vittorio Maurino:** Data curation; Investigation; Writing-review & editing. **Giuseppe Colella:** Data curation; Investigation; Writing-review & editing. **Raffaele Rauso:** Data curation; Investigation; Writing-review & editing. **lucio montebugnoli:** Data curation; Investigation; Writing-review & editing. **Davide B Gissi:** Data curation; Investigation; Writing-review & editing. **Mario Gabriele:** Data curation; Investigation; Writing-review & editing. **Marco Nisi:** Data curation; Investigation; Writing-review & editing. **Andrea Sardella:** Data curation; Investigation; Writing-review & editing. **Giovanni Lodi:** Data curation; Investigation; Writing-review & editing. **Elena Maria Varoni:** Data curation; Investigation; Writing-review & editing. **Amerigo Giudice:** Data curation; Investigation; Writing-review & editing. **Alessandro Antonelli:** Data curation; Investigation; Writing-review & editing. **Marco Cabras:** Data curation; Investigation; Writing-review & editing. **Alessio Gambino:** Data curation; Investigation; Writing-review & editing. **Paolo Vescovi:** Data curation; Investigation; Writing-review & editing. **Alessandra Majorana:** Data curation; Investigation; Writing-review & editing. **Elena Bardellini:** Data curation; Investigation; Writing-review & editing. **Giuseppina Campisi:** Data curation; Investigation; Writing-review & editing. **Vera Panzarella:** Data curation; Investigation; Writing-review & editing. **francesco spadari:** Data curation; Investigation; Writing-review & editing. **Sonia Marino:** Data curation; Investigation; Writing-review & editing. **Monica Pentenero:** Data curation; Investigation; Writing-review & editing. **Samuele Sutera:** Data curation; Investigation; Writing-review & editing. **Matteo Biasotto:** Data curation; Investigation; Writing-review & editing. **Margherita Gobbo:** Data curation; Investigation; Writing-review & editing. **Luca Guarda Nardini:** Data curation; Investigation; Writing-review & editing. **U. Romeo:** Data curation; Investigation; Writing-review & editing. **Gianluca Tenore:** Data curation; Investigation; Writing-review & editing. **Rosario Serpico:** Data curation; Investigation; Writing-review & editing. **Alberta Lucchese:** Data curation; Investigation; Writing-review & editing. **Carlo Lajolo:** Data curation; Investigation; Writing-review & editing. **Cosimo Rupe:** Data curation; Investigation; Writing-review & editing. **Massimo Aria:** Data curation; Formal analysis; Investigation; Methodology; Resources; Software; Supervision; Validation; Writing-review & editing. **Agostino Gnasso:** Data curation; Formal analysis; Methodology; Resources; Software; Writing-review & editing. **Michele Davide Mignogna:** Conceptualization; Investigation; Methodology; Supervision; Validation; Writing-original draft; Writing-review & editing.

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