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Relationship between Occurrence and Progression of Lung Cancer and Nocturnal Intermittent Hypoxia, Apnea and Daytime Sleepiness*

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Summary: The possible relationship between lung cancer and nocturnal intermittent hypoxia, apnea and daytime sleepiness, especially the possible relationship between the occurrence and progression of lung cancer and obstructive sleep apnea syndrome (OSAS) was explored. Forty-five cases of primary lung cancer suitable for surgical resection at the Third Affiliated Hospital of Kunming Medical University between January 2017 and December 2017 were recruited (lung cancer group), and there were 45 patients in the control group who had no significant differences in age, sex and other general data from lung cancer group. The analyzed covariates included general situation, snore score, the Epworth Sleeping Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), apnea and hypopneas index (AHI), oxygen desaturation index 4 (ODI_4), lowest arterial oxygen saturation [$LSpO_2$ (%)], oxygen below 90% of the time [T90% (min)], the percentage of the total recorded time spend below 90% oxygen saturation (TS90%), to explore the possible relationship between lung cancer and above indicators. The participants were followed up for one year. The results showed that: (1) There was significant difference in body mass index (BMI), ESS, AHI, T90% (min), TS90%, ODI_4, snore score and $LSpO_2$ (%) between lung cancer group and control group (P<0.05) . There was no statistically significant difference in age, gender, PSQI score, incidence of concurrent hypertension, diabetes and coronary heart disease (CHD), and smoking history between the two groups (P>0.05); (2) Patients in the lung cancer group were divided into OSAS subgroup and non-OSAS subgroup according to the international standard for the diagnosis of OSAS. There was significant difference in BMI, age, staging, incidence of concurrent hypertension and concurrent CHD, snore score, ESS score, T90% (min), TS90%, ODI_4 and $LSpO_2$ (%) between OSAS subgroup and non-OSAS subgroup (P<0.05) . There was no statistically significant difference in gender, PSQI score, incidence of concurrent diabetes, smoking history and lung cancer type between the two groups (P>0.05); (3) AHI was strongly negatively correlated with the $LSpO_2$ (%) and positively with ESS, staging, snoring score, T90% (min), TS90%, ODI_4 and BMI (P<0.05); (4) There were 3 deaths, 5 cases of recurrence, and 4 cases of metastasis in OSAS subgroup; and there was 1 death, 4 cases of recurrence and 2 cases of metastasis in non-OSAS subgroup during the follow-up period of one year, respectively. There was no significant difference in mortality, recurrence rate and metastasis rate between the two subgroups, and the total rate of deterioration in OSAS subgroup was significantly increased compared to the non-OSAS subgroup (P<0.05). It was concluded that the patients with lung cancer are prone to nocturnal hypoxemia, apnea, snoring and daytime sleepiness compared to control group. The incidence of OSAS in patients with lung cancer was higher, and the difference in the hypoxemia-related indicators was statistically significant. The mortality, recurrence rate, and metastasis rate increases in lung cancer patients with OSAS during the one-year follow-up period, suggesting that OSAS may be a contributing factor to the occurrence and progression of lung cancer.

Key words: lung cancer; nocturnal intermittent hypoxia; apnea; daytime sleepiness; obstructive sleep apnea syndrome

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Lung cancer is the leading cause of cancer death in the world, and the pathogenesis of lung cancer is still unclear. Some researchers reported lung cancer may be related to nocturnal hypoxemia and sleep apnea. Sleep apnea syndrome (SAS) is a disease with high incidence and serious harm to human health. Among them, obstructive SAS (OSAS) is a kind of disorder of sleep structure such as recurrent nocturnal apnea, chronic intermittent hypoxia, hypercapnia, and sympathetic nerve excitation, and accounts for more than 90% of SAS[1].

OSAS has been proved to deteriorate the function of target organs in the body, which may be related to the chronic diseases such as hypertension, coronary heart disease (CHD), diabetes, obesity and pulmonary hypertension, etc., especially cerebrocardiovascular diseases. Relevant clinical trials have indicated that OSAS is considered as an independent risk factor for diabetes, CHD, hypertension, and stroke[2, 3]. Previous studies have focused more on the effect of OSAS on normal people. It is well known that the occurrence of OSAS seriously affects the quality of life of patients. Epidemiologically, OSAS also increases the morbidity and mortality of tumors[4]. Li *et al*[5] found that OSAS is associated with the occurrence and progression of lung cancer to some extent, and the risk of lung cancer patients with OSAS is higher than normal people, however the correlation between them is not clear yet. We still need further study to observe the changes of indicators of nocturnal hypoxemia in patients with lung cancer, in order to improve the understanding of the correlation between lung cancer and OSAS, and provide help for the clinical treatment for such patients.

1 MATERIALS AND METHODS

1.1 General Condition

Forty-five cases of primary lung cancer suitable for surgical resection at the Third Affiliated Hospital of Kunming Medical University between January 2017 and December 2017 were recruited (lung cancer group), and there were 45 patients in the control group who had no significant differences in age, sex and other general data from lung cancer group. Patients in the lung cancer group were divided into OSAS subgroup (n=24) and non-OSAS subgroup (n=21) according to the international standard for the diagnosis of OSAS.

All patients agreed to participate in this study and signed the informed consent. The inclusion criteria were as follows: (1) normal range of blood pressure in patients with hypertension after use of antihypertensive treatment, and no hypertension-related complications; after symptomatic treatment, the patients with CHD were stable without complications; the blood glucose level in patients with type 2 diabetes without complications was normal after treatment; (2) no drugs possibly influencing the sleep patterns were currently being taken; (3) the patients having no mental retardation, normal language expression ability, and ability to judge their own situation and evaluate the relevant content involved in this study.

The patients suffering from the following diseases or lesions were excluded: intracranial lesions, infectious diseases, pulmonary embolism, rheumatic diseases and other diseases that may cause abnormal blood oxygen saturation.

1.2 Questionnaire for General Conditions

The analyzed covariates included age, height, weight, smoking history, tumor history and associated diseases.

1.3 Follow-up

The lung cancer participants were followed up for one year. The first follow-up time slot was 1 month after the operation, and telephone follow-up was conducted every 3 months thereafter. Endpoint events were defined as recurrence, metastasis, or death during the follow-up period.

1.4 Epworth Sleepiness Score (ESS), Pittsburgh Sleep Quality Index (PSQI) and Snore Score (SS)

For ESS, patients' daytime sleepiness was evaluated by 8 items, each of which was divided into 4 levels: score 0 to 3 for never dozing, mild, moderate, and very likely respectively. The higher the score, the more obvious the tendency of drowsiness. The sample was tested in a large population and proved to be clinically useful.

For PSQI, the sleep quality of the patient in the last one month was assessed by 18 self-assessment items, and 18 items were composed of 7 components. Each component was scored according to 0–3, and the cumulative score of each component was defined as PSQI total score. The total score ranged from 0 to 2l. The higher the score, the worse the sleep quality. This table has good reliability and validity, and can be used to effectively evaluate the sleep quality of patients before and after chemotherapy.

For SS, the severity of the patient's nocturnal snoring was assessed on a scale of a total score in 10. 0: no snoring; 1–3: slight snoring, not affecting the rest in bed; 4–6: moderate snoring, affecting the rest in bed; 7–9: heavy snoring, affecting the rest of the other people but your partner still shares a bed with you; 10: the roommate can't stand the snoring and you have to split the room. The higher the score, the more severe the snoring and the poorer the quality of sleep.

All subjects received philips YZB/USA 1575-2013 portable sleep recorder to monitor patients' sleep for at least 7 h per night. The subjects are not allowed to take a nap that day, and sedatives, morphine, alcohol and anti-inflammatory analgesics and other drugs which affect sleep are banned, and the oronasal airflow, breathing movement in chest and abdomen,

SpO_2, position and snore recorded. All data previously listed were played back, analyzed by a computer, and corrected artificially. The data about apnea hypopnea index (AHI), oxygen desaturation index (ODI_4), lowest arterial oxygen saturation [$LSpO_2$ (%)], oxygen below 90% of the time [T90% (min)], and the percentage of the total recorded time spend below 90% oxygen saturation (TS90%) were obtained.

1.5 Statistical Analysis

The statistical figure was drawn by GraphPad Prism 6.0. Measurement data were expressed as mean±standard deviations (SD), SPSS 20.0 software package was used for Spearman analysis, and the correlation coefficient was represented by *r*. $P<0.05$ was considered statistically significant.

2 RESULTS

2.1 General Data in Lung Cancer Group and Control Group

The body mass index (BMI) in lung cancer group was significantly increased compared to control group ($P<0.05$), but there was no statistically significant difference in age, gender, incidence of concurrent hypertension, diabetes and CHD, and smoking history between the two groups ($P>0.05$).

2.2 Scores of ESS, PSQI and Snore and Indicators of Hypoxemia in Lung Cancer Group and Control Group

The scores of ESS and snore, AHI, T90% (min), TS90%, and ODI_4 were significantly increased, and $LSpO_2$ (%) was significantly decreased in luncer cancer group as compared with those in control group ($P<0.05$). There was no statistically significant difference in PSQI score between the two groups ($P>0.05$, fig. 1).

2.3 General Data in OSAS Subgroup and Non-OSAS Subgroup

The BMI, and incidence of concurrent hypertension and CHD in OSAS subgroup were significantly increased compared to non-OSAS subgroup ($P<0.05$). but there was no statistically significant difference in gender, incidence of concurrent diabetes, smoking history and lung cancer type between the two groups.

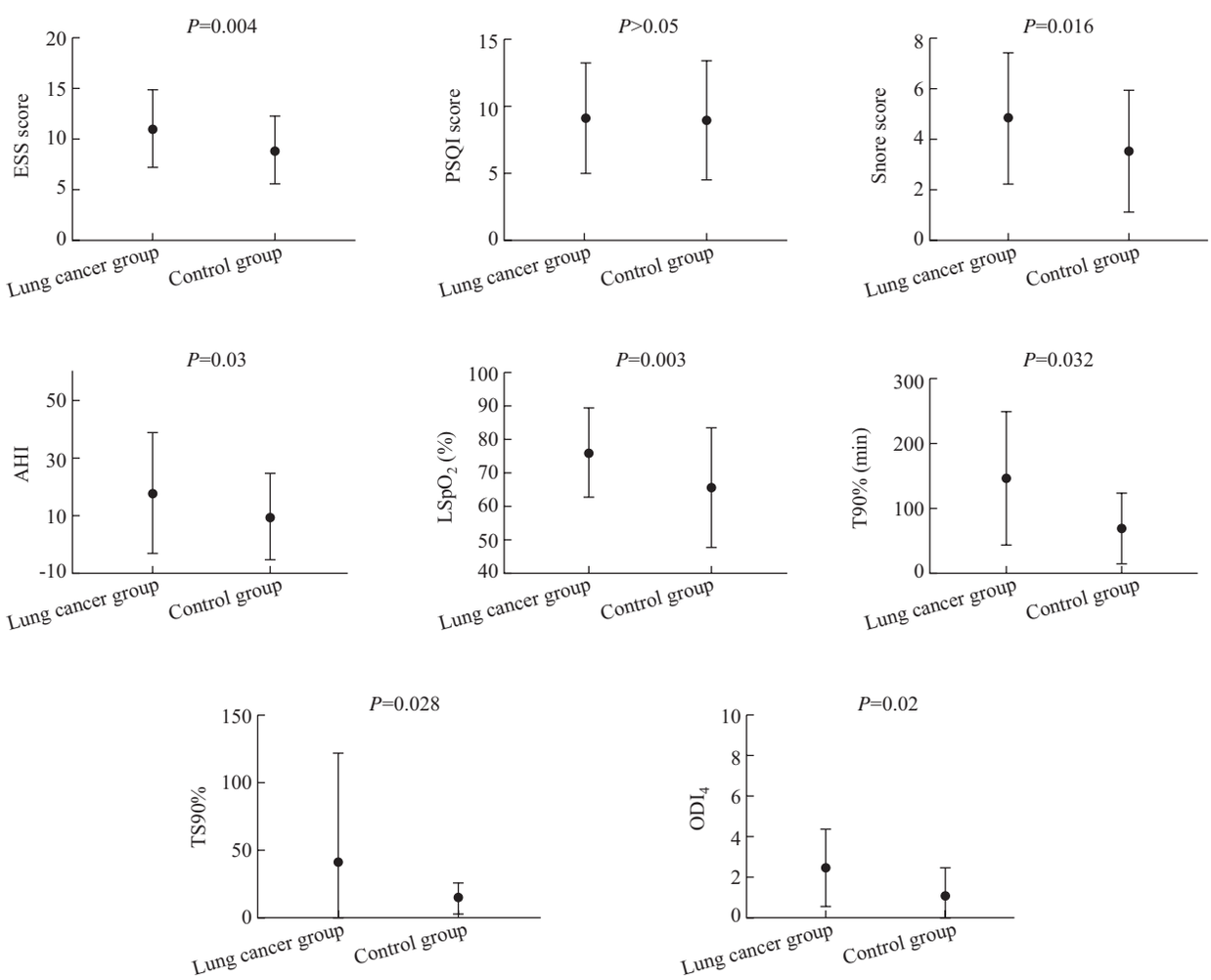

Fig. 1 Score of ESS, PSQI and snore, and indicators of hypoxemia in lung cancer group and control group

2.4 Scores of ESS, PSQI and Snore and Indicators of Hypoxemia in Two Subgroups

The scores of ESS and snore, T90% (min), TS90% and ODI_4 were significantly increased, and $LSpO_2$ (%) was significantly decreased in OSAS subgroup compared to non-OSAS subgroup (all $P<0.05$). There was no significant difference in PSQI score between two subgroups ($P>0.05$, fig. 2).

2.5 Correlation between AHI and Hypoxemia-related Indicators

The results showed AHI was strongly negatively correlated with $LSpO_2$ (%) and positively with ESS score, staging, SS, T90% (min), TS90%, ODI_4 and BMI ($P<0.05$). However, AHI was not correlated with gender, age, concurrent hypertension, diabetes and CHD, smoking history, lung cancer type, and PSQI score ($P>0.05$; fig. 3).

2.6 Follow-up Outcomes

Follow-up outcomes showed there were 3 deaths, 5 cases of recurrence, and 4 cases of metastasis in OSAS subgroup, accounting for 12.5%, 20.8%, and 16.7% respectively. There was 1 death, 4 cases of recurrence and 2 cases of metastasis in non-OSAS subgroup during the follow-up period of one year, accounting for 4.8%, 19% and 9.5% respectively. There was no significant difference in mortality, recurrence rate and metastasis rate between the two groups ($P>0.05$). There were 9 cases of metastasis or recurrence, and 10 deaths due to metastasis or recurrence in OSAS subgroup, accounting for 37.5% and 41.7% respectively. There were 5 cases of metastasis or recurrence, and 5 deaths due to metastasis or recurrence in non-OSAS subgroup, accounting for 23.8% and 23.8% respectively. The total rate of deterioration in OSAS subgroup was significantly increased compared to the non-OSAS subgroup ($P<0.05$).

3 DISCUSSION

In recent years, many countries have reported a significant increase in the incidence and mortality of lung cancer, but the mechanism of the occurrence and development of lung cancer has not been fully defined. Studies have shown that the risk of lung cancer patients with OSAS is higher than in general population with OSAS[6]. Evidence from relevant experiments also suggests an increased incidence of interstitial hypoxia and sleep disruption in lung cancer patients[7–9]. The increasing cancer incidence and mortality depends on the severity of hypoxemia which occurs during sleep-disordered breathing[10, 11]. Our study showed there was significant difference in BMI, ESS score,

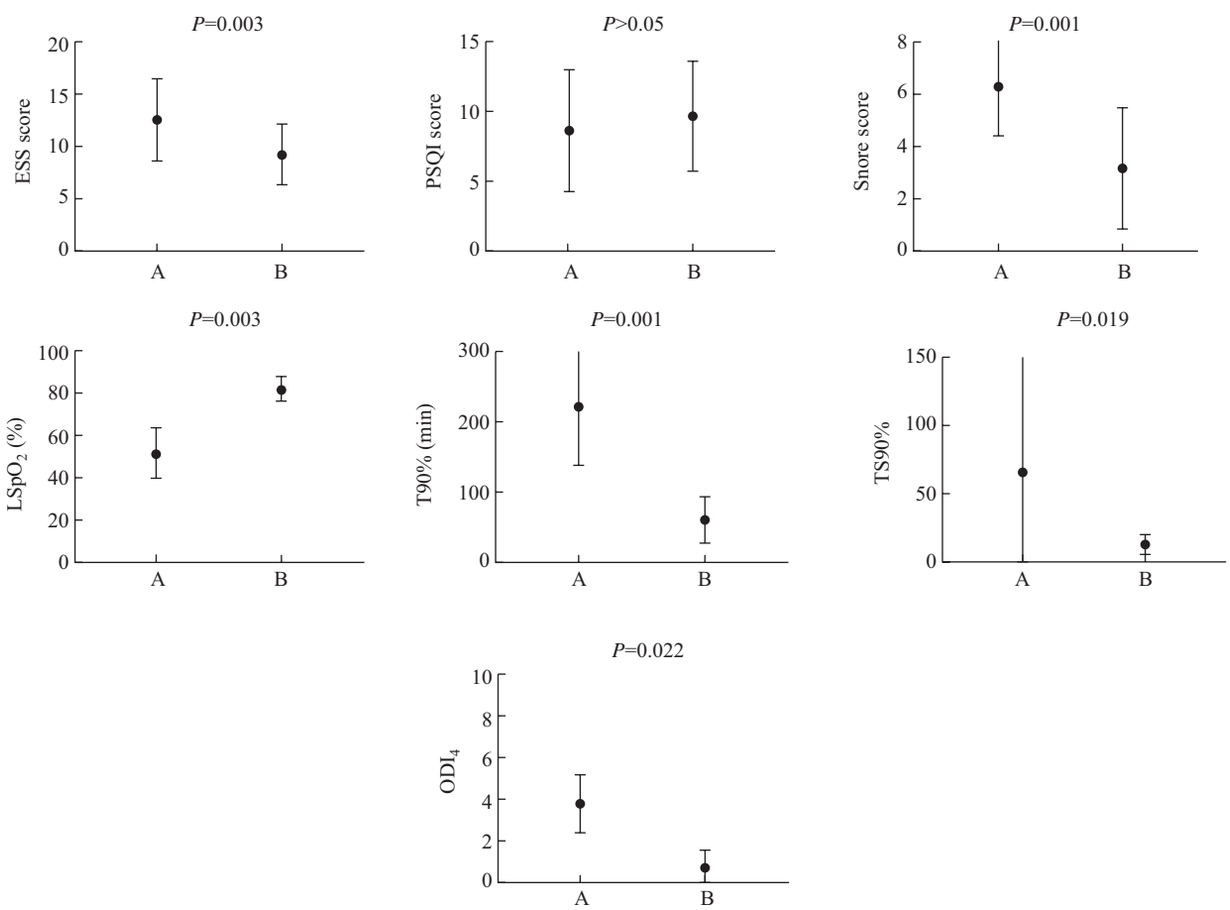

Fig. 2 Scores of ESS, PSQI and snore, and indicators of hypoxemia in OSAS subgroup (A) and non-OSAS subgroup (B)

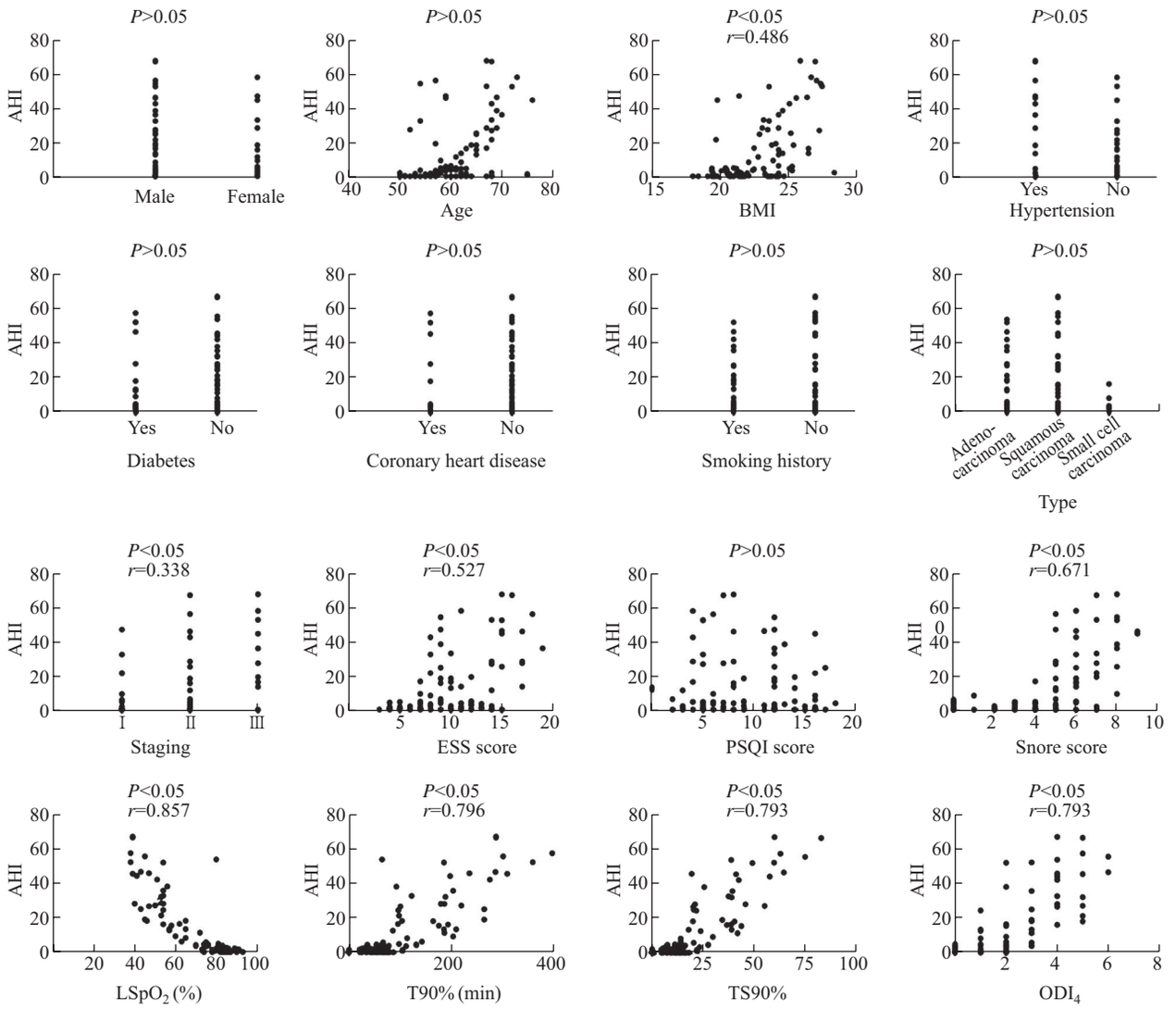

Fig. 3 Correlation between AHI and hypoxemia-related indicators

AHI, T90% (min), TS90%, ODI_4, SS between lung cancer group and control group (P<0.05), suggesting the lung cancer patients are more prone to suffer from nocturnal intermittent hypoxia, apnea, daytime sleepiness and other symptoms. On the one hand, lung cancer patients are easy to be affected in many ways, resulting in sleep disorders. Some researchers have found that the occurrence of sleep structure disorder in lung cancer patients is closely related to tumor compression and pain caused by tumor, because of the heavy psychological burden and side effects brought by chemotherapy. On the other hand, sufficient oxygen cooperation plays a crucial role in maintaining the normal function of cells, tissues and organs. Even in the absence of severe respiratory diseases which affects the oxygen transport of tissues, hypoxia is prevalent in tumor tissues resulting from high proliferation rate of cancer cells. When the rate of angiogenesis is slower than tumor growth, the amount of oxygen to the tumor to grow and metabolize can't be supplied sufficiently. In addition to continuous hypoxia in tumor tissues, vascular compression caused by abnormal growth of tumor also causes intermittent hypoxia to a certain extent in the area around the tumor. And any factors causing nocturnal intermittent hypoxia and apnea can induce OSAS.

Lung cancer can lead to a higher risk of OSAS. The Wisconsin Cohort study also shows a nearly five-fold increasing risk of cancer death due to severe sleep respiratory disorders[12]. Animal experiments confirms that after intermittent hypoxia treatment in mice, the total amount of circulating DNA in plasma significantly increases, while under hypoxia environment, the body will give priority to the proliferation of tumor cell DNA[13], and oxygen concentration is also significantly correlated with tumor size, mass and invasiveness, demonstrating that OSAS accelerates the progression of lung cancer in mice and enhances tumor

invasiveness[14], which is consistent with our findings. Our study suggests that tumor stage of lung cancer in OSAS subgroup was always more advanced than non-OSAS subgroup, and OSAS subgroup got higher incidence of nocturnal intermittent hypoxia, apnea and daytime sleepiness. In addition to hypoxemia, age is also shown to be a risk factor of OSAS in lung cancer patients. The incidence of OSAS increased with age in lung cancer patients, which might be related to the upper respiratory muscle relaxation that cannot fight the negative pressure produced in the process of breathing in the elderly patients. With the increase of age, various body functions gradually decline, and the reactivity and compensatory ability of the body gradually decrease, thus increasing the incidence of OSAS[15]. Therefore, for older patients with lung cancer, we should alert possibility of OSAS. In this study, there was significant difference in incidence of concurrent hypertension and CHD between OSAS subgroup and non-OSAS subgroup (P<0.05). Due to the occurrence of nocturnal hypoxemia and hypercapnia, central and peripheral chemoreceptors are stimulated, thereby stimulating the sympathetic nerves, leading to increased blood pressure after sleep and wakefulness at night in OSAS patients. In addition, a series of reactions including the activation of renin angiotensin system, endothelial injury, impaired blood pressure regulation and oxidative stress in OSAS patients can also lead to the increase of blood pressure, and the above process can lead to the occurrence of CHD by increasing the release of inflammatory factors such as endothelin 1 (ET-1). Previous studies have shown that OSAS is closely related to the occurrence of cardiovascular diseases, acts as an independent risk factor of CHD which is independent on race, age, smoking, gender and other factors, and can increase the incidence and mortality of CHD. Obesity is the most important risk factor for OSAS[16]. Obese people are more likely to develop OSAS due to upper airway stenosis caused by fat accumulation[17, 18], which is consistent with the results of our study. On the other hand, obese patients are at higher risk of cardiovascular diseases. Therefore, obesity and OSAS are mutually causal and mutually promoting, which jointly lead to the occurrence of cardiovascular diseases. In addition, relevant researches also reported that obesity was significantly related to the incidence and mortality of cancer. Obesity contributes to the body's chronic inflammatory response, which is part of the way all cancers evolve. Therefore, obesity may be the internal link between OSAS and lung cancer and cardiovascular disease, but the specific mechanism remains unclear, which requires further study.

The diagnosis of OSAS in this study was depended on the patient's AHI. There was significant difference in AHI between lung cancer group and control group (P<0.05). However, according to the analysis of the correlation between AHI values and various indicators, AHI was positively with staging (P<0.05). It is generally believed that the larger the tumor diameter and the later the tumor stage, the more severe the pressure on the lungs, and the greater the risk of hypoxemia and sleep disorders[19]. This study also confirmed the correlation between OSAS and lung cancer staging, but OSAS is not related to tumor differentiation. In view of this result, we believe that hypoxic microenvironment promotes the growth of lung-specific tumors, which has been confirmed by relevant studies in which intermittent hypoxia induces pulmonary metastasis of melanoma in OSAS patients[7]. Other evidence also suggests that the anoxic tumor microenvironment contributes to the development of non-small cell lung cancer[20]. *In vitro* studies further demonstrated that cultured lung cancer cells undergoing intermittent hypoxia were more resistant to radiation and apoptosis and more prone to metastasis[21]. It verified again that the risk of OSAS was increased in patients with lung cancer, and the occurrence of OSAS was also a contributing factor to the progression of lung cancer. This also explains the moderate positive correlation between AHI and ESS scores in lung cancer patients in this study. Hypoxemia, chronic fatigue, and daytime sleepiness are common symptoms of lung cancer patients, which may be aggravated with OSAS and may even be caused by OSAS in some cases.

At the end of the follow-up, there was no significant difference in mortality, recurrence rate and metastasis rate between the two subgroups, and the total rate of deterioration in OSAS subgroup was significantly increased compared to the non-OSAS subgroup (P<0.05). The results suggested that death, recurrence, metastasis and other malignant events in lung cancer patients with OSAS increased, and the concurrent OSAS may be a contributing factor to the development and progression of lung cancer. This is consistent with the follow-up results of cancer patients with OSAS in Wisconsin Cohort[6], suggesting higher mortality and shorter median survival time in lung cancer patients with OSAS than in those without OSAS. It also indicates that concurrent OSAS may be a promoter of lung cancer occurrence and progression. Another study on continuous positive airway pressure (CPAP) therapy in OSAS patients suggested that many tumor related genes including photo-oncogenes were down-regulated after 30 days of treatment in OSAS patients, while the expression of these genes was significantly up-regulated in OSAS patients without CPAP therapy[22]. It suggests that hypoxic environment plays a vital role in the progression of lung cancer. Currently, it is believed that the mechanisms by which OSAS accelerates the progression and invasiveness of lung cancer include: (1) oxidative stress: intermittent

hypoxia can increase the production of reactive oxygen species (ROS), which constitutes important stimulants for the activation of oxidative stress system. Oxidative stress destroys the stability of mitochondria by destroying DNA, RNA and lipids of the body, leading to gene mutation, cell growth and morphological changes, and eventually leading to tumorigenesis and inducing more aggressive cancer cell subtypes[23]; (2) hypoxia inducing factor (HIF): when continuous or intermittent hypoxia occurs in the body, HIF-1 especially HIF-1α increase is the main measures to cope with hypoxia. It is activated by triggering a series of angiogenic molecules produced by mechanisms to compensate for lack of oxygen. One of the most important factors is vascular endothelial growth factor (VEGF). VEGF can stimulate the generation of tumor angiogenesis, and provide favorable condition for the growth of tumor cells; (3) systemic inflammation: in OSAS patients, there is usually a local or systemic inflammatory reaction. When there is an inflammatory reaction, the body will be out of balance in oxidation/antioxidation. ROS increases and proinflammatory substances such as TNF-α, IL-6 and IL-8 also increase. These added substances play a role in promoting the occurrence and development of tumors, therefore, OSAS as a proinflammatory factor, explains the possible association between OSAS and tumors to some extent; (4) changes in sleep structure: Hakim found in the mouse model of sleep disorder that increased sympathetic excitability during sleep arousal would lead to increased catecholamine release[24]. The function of many tumor stromal cells is regulated by β receptors and their subtypes, including epithelial cells and vascular cells, which are of great significance for the growth and metastasis of tumors[25].

As mentioned above, the pathobiology of OSAS is complex. In addition to intermittent hypoxemia, hypercapnia and sleep disruption, there are also effects such as enhancing sympathetic nerve activity, which can be involved in cancer progression by regulating gene expression, inflammation and angiogenesis, all of which may play an important role in the occurrence of cancer. Therefore, active control of intermittent hypoxia in lung cancer patients is of great clinical significance in improving the therapeutic efficacy and quality of life of these patients.

Based on the chronic injury caused by OSAS to various systems such as cardiovascular system and respiratory system, the United States guideline has classified OSAS as a chronic disease. In addition, OSAS patients have been observed to result in abnormal glucose and lipid metabolism in clinic, leading to increased risk of complications of other diseases such as diabetes. However, no statistically significant difference in relevant indicators has been found in our study, which may be related to the small sample size of this study and certain errors caused by our inclusion criteria. Therefore, there are still some limitations in this study, such as small sample size, a relatively poorer accuracy of portable sleep monitoring than polysomnography monitor. Therefore, further studies are still needed.

In conclusion, although our data strongly suggest nocturnal hypoxemia, apnea, snoring and daytime sleepiness in lung cancer group significantly increased compared to control group, and the OSAS subgroup is prone to nocturnal hypoxemia, apnea, snoring and daytime sleepiness compared to non-OSAS subgroup, the mechanism of nocturnal hypoxemia, apnea, snoring and daytime sleepiness inducing the deterioration of lung cancer is still unclear. In addition, the insufficient number of cases may affect the results of the study. Therefore, further large-scale multi-center studies are still needed to clarify the relationship between lung cancer and OSAS and the influence of OSAS on the prognosis of lung cancer patients, so as to further improve the quality of life of lung cancer patients and even prolong the survival time.

Conflict of Interest Statement

All authors declare that they have no conflict of interest.

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