A NARRATIVE REVIEW AND LONGITUDINAL DATA ANALYSIS METHOD TO

EVALUATE THE ASSOCIATION BETWEEN HEAD AND NECK CANCER AND

OBSTRUCTIVE SLEEP APNEA

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The Supervisory Committee certifies that this ***disquisition*** complies with North Dakota

State University's regulations and meets the accepted standards for the degree of

MASTER OF SCIENCE

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ABSTRACT

The pathophysiological mechanisms of obstructive sleep apnea (OSA) and Head and Neck cancers (HNC) have not been fully investigated. Currently, investigating the relationship between HNC and OSA is incomplete due to the restriction of histological, molecular, and clinical evidence. In this research, the first section reviews the common course of therapy in patients with HNC with OSA, the causation and association between HNC and OSA, and summary of statistical methods used to investigate these relationsip. The review study suggests that more rigorously designed studies with longitudinal data collection should be considered. The second section concentrate on developing a longitudinal data analysis method that determines the change over time of Apnea-Hypopnea index (AHI) in OSA patients and estimate the effect of treatment on these changes. By successfully address the change of AHI of patients undergoing the cancer treatment, the management of cancer and OSA in adults may be improved and developed.

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DEDICATION

I dedicate my thesis to my lovely family and especially thank to my friends: Vikneshwari Natarajan, Quyen Hoang, Srilakshmi Gayatri Gundlakunta, Nguyen Ngoc Thao Quyen, Le Xuan Hieu, Tran Minh Phuong Nam, Thang Bui, Cha La 122 team, 218 room for always willing to support me and encourage me to finish this thesis.

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LIST OF ABBREVIATIONS

HNC ....Head and Neck cancer

OSA...Obstructive sleep Apnea

BIC... Bayesian Information Criterion

R^2 ....R-squared statistic

Adjust R^2 ....Adjusted R-squared statistic

AIC...Akaike information criterion

LogLik...Log-likelihood value

HR...Hazard ratio

CI...Confidence interval

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1. INTRODUCTION

Sleep disturbance is a noticeable problem of cancer patients with the most frequently reported symptoms being fatigue, leg restlessness, insomnia, and excessive sleepiness. More specifically, in Head and Neck cancer patients, obstructive sleep apnea (OSA) is a common complaint and OSA severity needs to be fully monitored. OSA is a type of sleep-related breathing disorder with a prevalence ranging from 3% to 7% of the adult population [1]. It is characterized by the derangements that occur due to repetitive collapse of the upper airway and often requires lifelong care or specific treatment such as positive airway pressure therapy to improve this disorder. In clinical, diagnostic criteria for OSA are based on clinical sleep evaluation including the recording of the number of occurrences of daytime sleepiness, snoring, witnessed breathing interruptions, or awakenings, and physical examination. To reduce the OSA severity, it is recommended that patients should receive timely treatment such as oral appliance therapy, continuous positive airway pressure (CPAP), or hypoglossal nerve stimulation (HNS).

There are many longitudinal studies were developed to estimate the change of OSA over a long duration. As mentioned, OSA leads to several adverse, such as obesity, diabetes, hypertension, cardiac, and cancer. In terms of OSA and obesity, it is considered a significant risk factor for the development and progression of OSA so many longitudinal studies that examine the effect of weight loss on OSA severity were conducted [2-4]. Likewise, the association between OSA and retinopathy in patients with Type 2 Diabetes was measured through long-term studies [5-7]. A study of 709 participants over 4 years suggested that the chance of having hypertension in people with mild and severe sleep-disordered breathing is 2 and 3 times more than normal people, respectively [8]. Using a remarkable 25-year follow-up data on 36963 individuals in Finland, another research showed that OSA significantly increased the risk for

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coronary heart disease in the general population (HR=1.36, p=0.0014, 95% CI 1.12 to 1.64) [9]

Lastly, many longitudinal studies were applied to analyze the association between OSA and

cancer, resulting in no significant relation [10]. Therefore, longitudinal data of OSA patients will

be used to be deeply investigated in this thesis.

In Head and Neck cancer patients with OSA, the consequences of untreated OSA can

initiate malignant transformation, hasten tumor proliferation, increase metastasis invasion, and

increase patient mortality [11-15]. The use of opioid medication in cancer curative-intent therapy

induces respiratory depression at night[16]. Other causes, including sedatives, narcotics,

radiotherapy, and chemotherapy, increase the risk of hypoventilation and OSA. Several possible

reasons cause sleep disruption in patients with tumors in the head and neck region. These include

cancer itself, medical therapy, psychosocial disturbances, and comorbid medical issues.

Therefore, several confounders should be considered to investigate the relationship between

OSA and head and neck treatments themselves. In this thesis, I concentrated on investigating this

association to provide more significant information for doctors in deciding on suitable treatment

for HNC patients.

Besides the clinical knowledge and study design, the evaluation method and modeling of

the clinical information should be considered to observe all valuable information from these

experiments [17]. One of the most critical steps to developing an optimal clinical model is to

perform a variable selection process. Variable selection means filtering irrelevant variables and

keeping the approximate ones, resulting in a set of variables that simplify and fit the model

perfectly. To reduce the variables in the dataset, the candidate variables, which have been

predicted or proven to have impacted the outcome, will be chosen first, using clinical knowledge

or searching information through literature and experts. Next, several variable selection methods

(Backward Elimination, Forward Elimination, Stepwise Selection, and All-possible Subset

Selection, will use to set thresholds to significantly collect outcome-related candidate variables.

The parameter selection for this method is dependent on the number of variables input as well as

the characteristic of clinical data. In addition, without this step, it can cause overfitting in the

prediction model and maintain the stability of the model when capturing the personal and group

characteristics of clinical data.

Besides the feature selection, the type of prediction model should be defined carefully.

According to the type of dependent variable (continuous or categorical variable), linear

regression or logistic regression models are identified. In this research, I am interested in the

change rate of AHI over time so a linear regression model is choosen.

2. BACKGROUND

In order to investigate the relationship between HNC and OSA, the mutual connections from the anatomical, pathological, and clinical care points of view are described. According to the anatomical distribution of the tumor site, it is showed that 90% of HNC tumors begin in the upper airway [18]. Likewise, OSA is caused by the repetitive collapse of the pharyngeal airway during sleep. The development of neoplasm in these regions causes a reduction in upper airway dimensions and an increase in airflow resistance that leads to the progression of OSA. In contrast, OSA establishes the repeated intermittent hypoxia environment which triggers the malignant transformation, growth, and metastasis of cancer. The following paragraphs provide background on the OSA diagnosis, and treatment and HNC anatomy, the tumor stage and HNC cancer treatment.

2.1. Anatomy of head and neck cancer region

As mentioned, the upper airway is an overlap area of HNC and OSA. The cancer site is a vital factor to decide the therapy for a cancer patient. Therefore, anatomic structures of head and neck regions (Figure 1) are considered as a key feature to explain the relationship between treatment and OSA.
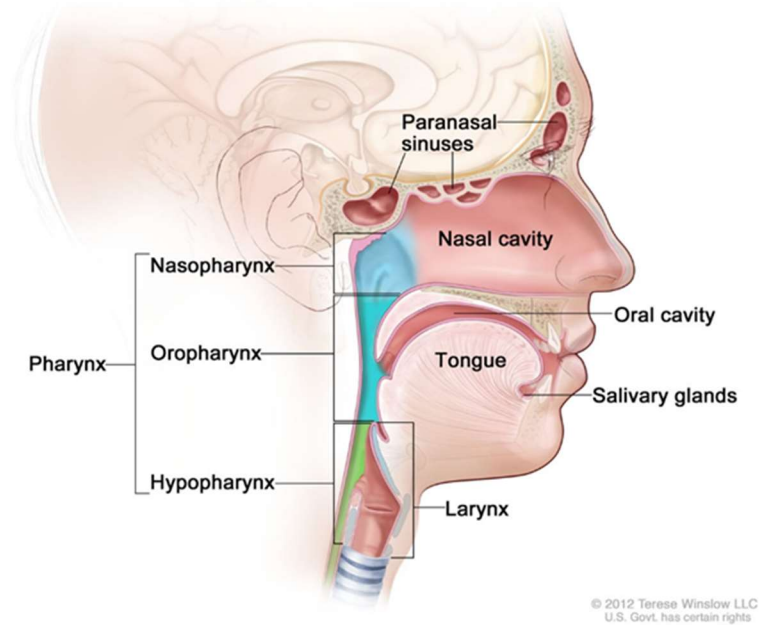
Figure 1: Illustrate the HNC location of paranasal sinuses, nasal cavity, oral cavity, tongue, salivary glands, larynx, and pharynx (including the nasopharynx, oropharynx, and hypopharynx).

2.1.1. Nasal cavity and paranasal sinuses

The nasal cavity is the beginning of the upper airway and locates between the oral cavity and the skull. It is divided into two main cavities by the nasal septum- a thin wall of bone and cartilage in the center of the nose. The nasal cavity is surrounded by four paranasal sinuses (maxillary sinuses, frontal sinuses, ethmoid sinuses, and sphenoid sinuses) which are small hollow spaces in the bones of the nose in terms of cancer in the nasal cavity, the typical symptoms are nasal obstruction, epistaxis, or obstructive pansinusitis early during the disease. The maxillary sinus is the largest of the paranasal sinuses which are present on each side and lie in the body of the maxilla. It has a pyramidal shape and forms a part of the lateral wall in the nasal cavity. The ethmoid sinus is located between the upper part of the nasal cavity and orbits. Superoanteriorly, the frontal sinus is found in the frontal bone and forms the lower part of the forehead and reaches over the eye sockets and eyebrows. The sphenoid sinus locates in the sphenoid bone, which is behind the nose between the eyes. Primary tumors in paranasal sinuses

seldomly produce significant symptoms. Because these sinuses are contained within the bony spaces so until the development of tumors can break the bone in the involved sinus cavity or cause obstruction, it is rare to be found in the early stage.

2.1.2. Oral cavity

The oral cavity is the beginning of the digestive system. It is located from the vermilion borders of the upper lip to the junction of the hard and soft palates and the borders of the lower lip. Within the area of the oral cavity are the lips, buccal mucosa, alveolar ridges with teeth and gingiva, retromolar trigone, the floor of the mouth, anterior two-thirds of the tongue, and hard palate. Because the oral cavity is lined by the oral mucosa which has a stratified squamous epithelium so the primary tumors in the mucosal surface of the oral cavity are variable and the majority of oral cancers arise in the squamous cells, which line the mouth, tongue, gums, and lips. For instance, tumors may be exophytic, endophytic, or ulcerative or it is a superficial proliferative lesion that leads to patients with mouth cancer typically presenting with a painful ulcer.

2.1.3. Larynx

The larynx (voice box) is one of the most common Head and Neck cancer sites. It locates at the third (C3) to six (C6) cervical vertebrae. The larynx skeleton is formed by a group of cartilages that are connected by ligaments and fibrous membranes. Due to it communicating with the pharynx superiorly and with the trachea inferiorly, the larynx performs three unique functions: passage for air, sphincter, and phonation. As larynx responses for three main roles, it may be divided into three main areas: supraglottis, glottis, and subglottis. The supraglottis lies above the vocal cord and contains epiglottis- a small flap of tissue that covers the larynx when swallowing and preventing food and fluids from going into the trachea and lungs. Glottis

includes the vocal cords which vibrate when air passes through them to produce the sound of the voice. The subglottis is the area below the vocal cords leading to the trachea. It is limited from the undersurface of the true vocal cords to the inferior border of the cricoid cartilage. In general, most laryngeal malignancies are squamous cell carcinomas. Patients with primary tumors at the larynx usually present with complaints of hoarseness of voice, respiratory obstruction, and hemoptysis dysphagia.

2.1.4. Pharynx

The pharynx is a long hollow tube that starts behind the nose and leads to the esophagus and the trachea. It is divided into three major parts the nasopharynx, oropharynx, and hypopharynx. The nasopharynx is the most superior and largest portion of the pharynx continuing to posterior of the nasal cavity. It is limited by the skull base and the sphenoid and laterally by the paired tori of the eustachian tubes. Patient with a tumor at the nasopharynx typically has several symptoms such as Presenting symptoms of neck mass, epistaxis, nasal obstruction, otalgia, and decreased hearing. The oropharynx is the middle part of the pharynx which extends from the soft palate to the epiglottis and contains tonsils. The initial symptoms of oropharyngeal cancer are often ambiguous, so it is hard to early diagnose. The hypopharynx is the inferior part of the pharynx. It connects the oropharynx superiorly to the larynx and esophagus below. Patients with hypopharyngeal cancer usually present with odynophagia, discomfort in the throat, and dysphagia.

2.1.5. Salivary gland

Salivary glands are exocrine glands that help to swallow and talk, and also protect the mouth and teeth. There are three pairs of major salivary glands: parotid glands, submandibular glands, and sublingual glands. Minor salivary glands are allocated in the oral cavity and

oropharynx. Tumors can develop in the major or minor salivary glands. The parotid glands are the largest of the major salivary glands which lie in front of the ears. In the parotid gland cancer typically presents round tumors, with a tendency to nodularity as they grow the tail of the gland such as the Warthin tumor. The submandibular glands are located in the anterior triangle of the neck. The sublingual glands are the smallest major salivary glands that lie under the tongue. Typically, patients with cancer in salivary glands present with a lump or swelling on or near your jaw or in your neck or mouth, Numbness in part of the face, and difficulty swallowing.

2.2. Tumor stages, and cancer treatments

Staging the tumor is important for cancer diagnosis and treatment strategies. According to the American Joint Committee on Cancer (AJCC), head and neck tumors are classified based on three characteristics of tumor growth: the size of the primary tumor (T), the involvement of regional lymph nodes (N), and the distant metastasis (M) as shown in **Table1**. In general, primary tumors are graded by increasing size from T0 to T3 while T4 describes the moderately advanced invasion of the tumor. Regional lymph nodes are classified from N0 to N3 by size (≤ 3, ≤ 6 cm, or > 6 cm), number (single or multiple), and location (ipsilateral, contralateral, and cervical lymph nodes). Distant metastasis is indicated by the M0 (absence) or M1(presence) referring to the detection of distant metastases. Manually, this classification might vary according to the specific anatomic site of the tumor and some additional factors. In particular, the UICC/AJCC 8th edition TNM Classification (TNM-8) introduced the separate clinical (cTNM) and pathological (pTNM) stage classifications for human papillomavirus (HPV) medicated oropharyngeal carcinoma[19]. Consequently, the more coherent the staging HNC tumor, the more accurate in prognostic outcome and survival rate especially in designating the course of therapy and their effects.

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Table 1: TNM staging system

Stage	T category	N category	M category	TNM combinations
I	T1: Tumor ≤ 2cm	N0: no regional lymph node metastasis	M0	T1 N0 M0
II	T2: Tumor ≥ 2cm <4cm	N0: no regional lymph node metastasis	M0	T2 N0 M0
III	T3: Tumor ≥ 4cm	N1: Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension	M0	T3 N0 M0 T1/T2 /T3 N1 M0
IVa	T4a: Tumor invades skin, mandible, ear canal, and fascial nerve	N2a: Metastasis in a single ipsilateral lymph node, > 3cm but ≤6cm N2b: Metastasis in a multiple ipsilateral lymph node, none >6cm N2c: Metastasis in a bilateral or contralateral lymph nodes, none >6cm	M0	T4a N0 /N1 M0 T1 /T2 /T3 /T4a N2 M0
IVb	T4b: Tumor invades skull base and/or pterygoid plates and/or encases carotid artery	N3: Metastasis in a lymph node >6cm in greatest dimension	M0	T4b Any N M0 Any T N3 m0
IVc	Any T	Any N	M1	Any T Any N M1

Three majors curative HNC therapies are surgery, radiation, and chemotherapy. Surgery is the common treatment for oral cavity squamous cell carcinomas (OCSCCs) and advanced stage (III-IV) laryngeal and hypopharyngeal cancers. The principal approach is to remove the primary tumor completely, along with the removal of any involved lymph nodes or lymph node groups. If the excision surgery requires a major tissue removal, the patient will receive reconstructive surgery to preserve the functions of the head and neck area by using a combination of skin, muscle, and occasionally bone to rebuild the removed area. Therefore, the surgical patients typically have several side effects which depend on the type and location of the

surgery including swelling of the mouth and throat area, and difficulty chewing or swallowing. These side effects will lead to difficulty in breathing and may affect the severity of OSA. In contrast, radiation and chemotherapy are the preferred treatments for laryngeal and pharyngeal cancers because they can help maintain the normal function of these regions. Radiation treatment is the use of a controlled dose of radiation to kill or damage neoplasm cells and is typically considered a major treatment for the early stages of cancer. Besides, it can be used as an adjuvant treatment after surgery to destroy remaining cancer cells and reduce the risk of cancer recurrence. Chemotherapy uses drugs to kill or slow the growth of tumors. It will affect cells at specific stages of a cycle of cells and does not differentiate between cancerous cells and healthy cells. Thus, patients undergoing chemotherapy are more susceptible to the side effects such as nausea and hair loss during treatment. Manually, patients with HNC typically treated by chemoradiation therapy which is a combination of radiotherapy, and it can be the main treatment or an adjuvant treatment after surgery. Unlike with the main treatment, the doses for adjuvant treatment are determined by the pathologic information obtained after the patient received the primary treatment. In addition, the clinical interpretation shows that long-term and late effects of these treatments are the potential to cause OSA or amplify OSA risk. For example, primary radiation and chemotherapy cause long-term swelling of the tongue and larynx while reconstructive surgery can compromise, and restrict the airway [20]. In addition to the tumor stage, the choice of HNC treatment is also based on the location, comorbidities, side effects, and patient desires [21]. Assessing the relationship between side effects after treatment especially recognizing the difficulties in the upper airway and OSA is necessary to manage the risk in HNC survivorship.

Besides mentioned therapies, there are some new treatments for patients with HNC such as targeted therapy, immunotherapy, and gene therapy. However, these new approaches are considered neoadjuvant therapies and need to be further evaluated and validate through clinical trials. Therefore, this review is just considering the relationship between surgery, radiotherapy, and chemoradiotherapy in HNC and OSA

2.3. OSA severity and treatments

According to the American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events, the severity of OSA was determined by an index – Apnea-Hypopnea Index (AHI) or Respiratory Disturbance Index (RDI). It is categorized by fewer than 5 apnea and hypopnea events per hour as normal, 5-15 events per hour as mild, 15-30 events per hour as moderate, and 30 or more events per hour as severe [22]. The OSA treatment strategy should be adjusted to the OSA severity with the consideration of the patient's co-morbidities. In mild to moderate OSA, oral appliances are preferred; however, if the patients get dental or cardiovascular risks, continuous positive airway pressure (CPAP) might be a favorite option. In contrast, CPAP is the induction treatment for severe OSA and should receive immediately. In case of failure therapy, especially in moderate to severe OSA, hypoglossal nerve stimulation (HNS), upper airway surgery, and maxillofacial surgery are recommended. In this paper, we will base on these criteria to evaluate the severity of OSA in HNC.

3. A REVIEW OF THE RELATIONSHIP BETWEEN HEAD AND NECK CANCER AND OBSTRUCTIVE SLEEP APNEA: CLINICAL STUDY AND STATISTICAL ANALYSIS

3.1. Abstract

Patients with Head and Neck cancers (HNC) and obstructive sleep apnea (OSA) experience commonly developed physical and psychological impacts. HNC and OSA occurred in the upper airway regions and established complex correlations. Throughout last decades, many studies that investigated the relationship between these upper airways suggested the increasing cases of OSA in the HNC population and the association between HNC surgery and OSA severity. However, developing precise strategies for therapeutic intervention as well as maintaining the clinical improvement of patients with HNC and OSA, requires more understanding of general relationship between HNC and OSA. Particularly, the pathophysiological mechanisms and evaluation strategies should be investigated comprehensively. Here, this paper aims to review the current course of HNC therapy, the observed causal and associate relationships in patients before and after receiving therapy, and data analytic methods that quantify the interactions between HNC and OSA in clinical research. In particular, our research obtained a positive correlation between AHI and primary tumor size was observed. Included case studies also illustrated new evidence that lipoma and tumors in the head and neck lead to OSA while sleep apnea surgery can develop the presence of tumor in treated region. Apart from clinical observations, these findings implicated several statistical methodologies to address the relationship between HNC and OSA in a single research and systematic review. Taken together, discovering the relationship between HNC and OSA is still incomplete due to the restriction of histological, molecular, and clinical evidence. In the future, more rigorously designed studies with longitudinal data collection should be considered.

3.2. Introduction

Cancer patients with comorbidities have suboptimal treatment outcomes and lower survival rates because of the negative effects caused by comorbid conditions [23]. One of the underdiagnosed and undertreated cancer comorbidities that need greater recognition is sleep-disordered breathing, especially obstructive sleep apnea (OSA). Among cancer patients, Head and Neck cancers (HNC) are the prioritized group of patients whose OSA severity needs to be fully considered [24,25]. The use of opioid medication in cancer curative-intent therapy induces respiratory depression at night [16]. Other causes, including sedatives, narcotics, radiotherapy, and chemotherapy, increase the risk of hypoventilation and OSA [24]. The most common consequences of untreated OSA are frequent episodes of hypoxia, irregular arousals, and fragmented sleep [26]. It has been shown that fragmented sleep and intermittent hypoxemia in OSA can initiate malignant transformation, hasten tumor proliferation (add the typical relationships with Head and Neck cancer), increase metastasis invasion, and increase patient mortality [11-15].

Although the relationship between OSA and HNC has been observed in clinical research, a systematic review of the comorbidity and statistical methods to quantify the disease associations base on the clinical observations has not been fully investigated. Several studies have been reported on HNC and OSA. Particularly, three of them [27-29]reviewed the association of tumor stage, cancer treatment, and OSA in the population with HNC. The others mentioned the relationship between fatigue, OSA, and HNC [25]] and summarized the missing diagnosis of OSA caused by tumors in the head and neck region[30]. Despite those excellent reviews, they mainly focused on determining the association rather than causal and sequential interactions between HNC and OSA. There was no study that mentioned OSA therapies that might be

tailored to HNC and the mutual impact of HNC on OSA. Consequently, this review targets to obtain the change of AHI under HNC conditions.

In this study, we concentrate on elaborating on the mutual relationships between HNC and OSA and summarize the statistical analysis of the association in previously reported clinical studies with the focus on three thematic questions:

- What is the alternative course of therapy for patients with HNC and OSA?

- Is there any relationship between HNC and OSA (including causal and associate interactions) and the physiological mechanism behind them (observed or non-observed)?

- What statistical methods were performed to analyze clinical data and the rationale to choose these methods?

3.3. Method

The review of the literature was conducted using PubMed, Google Scholar, Web of Science, Microsoft academic, Semantic, Europe PMC, Scopus, and Crossref databases to collect articles related to OSA in patients with HNC. The final data met these publishing criteria: peer-reviewed publication in English from 2010 to May 2022 with full-text accessibility. The specific level of evidence is considered in this review. Level of evidence criteria is assigned to grade the studies based on the methodological quality of study design, validity, and application to patient care. The used grading scheme is guided by the system of the Oxford Centre for Evidence-based Medicine for ratings of individual studies [31]. The higher level of evidence represents the strength of recommendation. The approach rates the level of evidence from 1 to 5, with 1 being the strongest clinical evidence and 5 being the weakest clinical evidence.

3.4. Results

The primary record includes 3122 articles from PubMed (n=172), Google Scholar (n=436), Web of Science (n=164), Microsoft academic (n=272), Crossref (n=500), Semantic (n=71), Europe PMC (1367), and Scopus(n=140) databases. Due to the limitations of the search engine, our study conducted a title screen following the MeSH term and synonym of Head and Neck Neoplasms and OSA: OSA OR Head and Neck cancer OR neoplasm OR tumor OR mass OR malignant OR carcinoma OR lymphoma. After screening, 305 articles were included, and 278 articles that were duplicated and not relevant to HNC and OSA are excluded. Because of some minor differences in title format, this step was designed after title screening to increase the accuracy in finding duplicate articles and unrelative articles. Among the 27 remaining studies, 3 articles were removed by: systematic review without meta-analysis, did not mention OSA assessment; and the final database included 25 studies. The summary of the review scheme was illustrated in Figure 2.
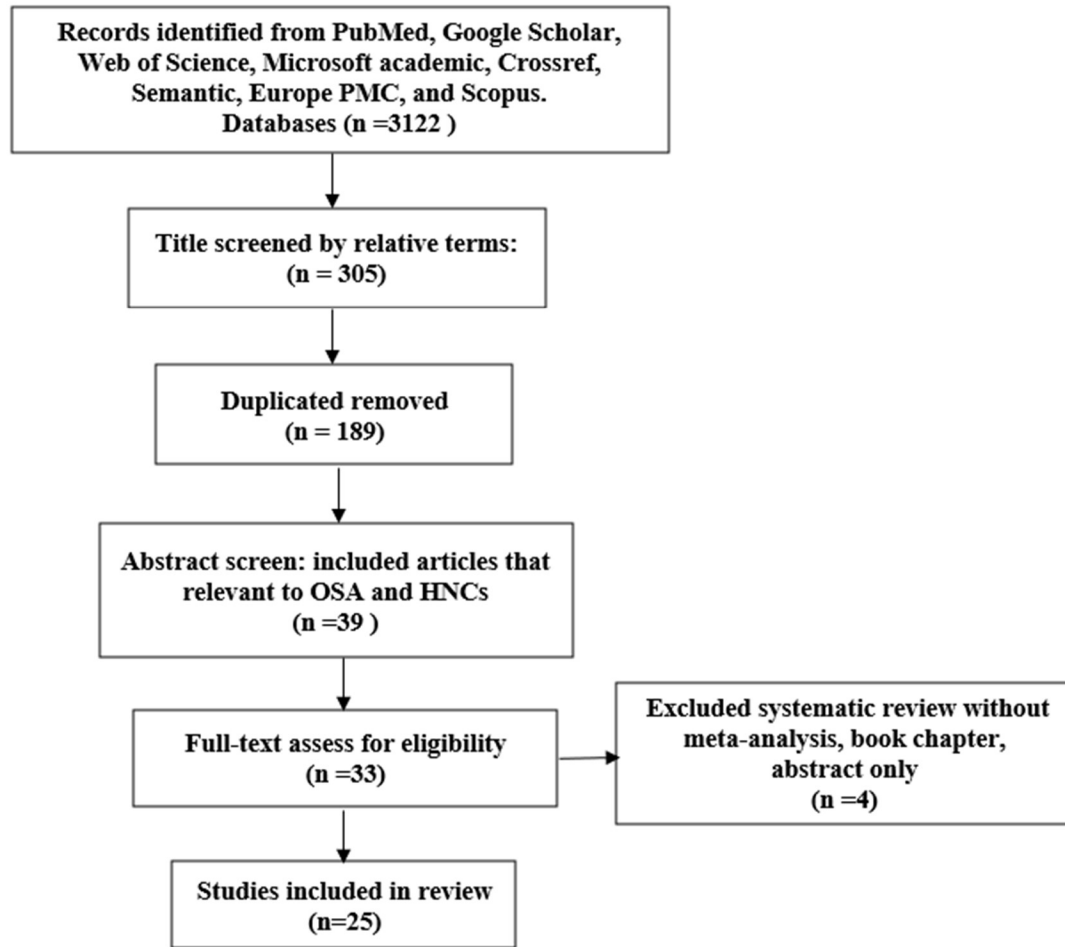
Figure 2: Scheme showing process of review and data inclusion

3.4.1. The characteristic of included papers

Among 25 included studies, 23 clinical studies were reviewed to investigate the course of therapy in HNC patients with OSA and the relationship between HNC and OSA, and 2 systematic and meta-analysis exams the interaction between OSA and HNC.

3.4.1.1. Clinical study

Most studies reported OSA severity in patients after treating HNC. Totally, there were 382 patients participating in this review. The participants are adults from 24 years to older with a mean BMI that was 27.6, the proportion of males also greater than females (except case report). The majority of articles are cross-sectional accounted 41%, 36% were case reports, and

prospective cohort studies were 23%. Seventeen of 22 studies were graded at level 4 of evidence (cross-sectional and case report) and 5 remaining studies were rated at level 2. These articles were published from 2010 to October 2021 in the United States (5), Italy (3), Taiwan (3), France (2), Korea (2), China (2), Brazil (1), Canada (1), Israel (1), Germany (1), Belgium (1) (**Table 2**).

3.4.1.2. Systematic review and meta-analysis

Besides 23 clinical studies, 2 systematic reviews with meta-analysis[18, 50] were evaluated to identify the scope of statistical methods that were conducted in examining the interaction between OSA and HNC. One reported the prevalence of OSA in HNC population (n=2315)[50]. Other study estimated the association between OSA and radiotherapy in HNC patients (n=268)[18]. The data were observed in patients from 24-87 years with 76% male and 24% female (**Table 2**).

Table 2: Summary characteristic of included studies

Study	Country/Year	Study Design	Level of Evidence	n	Age, Mean, (range),years	Male/ Female n/n	BMI, Mean (range), kg/m²	Measure at Pre/Post-cancer treatment
Casale et al[32]	Italy/2012		4	1	70	1/0	38	Pre and Post
Asai et al[33]	Japan /2013		4	1	71	0/1	33.4	Pre and Post
Kim et al[34]	Korea /2015		4	1	60	0/1	NA	Pre
Piccin et al[35]	Italy /2016	Case-report	4	2	49.5 (47- 52)	2/0	21.5(21- 22)	Post
Zheng et al[36]	USA /2017		4	1	64	1/0	24.4	Post
Pierre et al[37]	France /2018		4	1	50	1/0	24.5	Post
Park et al[38]	Korea /2020		4	1	59	1/0	NA	Pre and Post
Hoshal et al[39]	USA /2021		4	1	71	1/0	28.75	Post
Qian et al[41]	Canada/2010		4	24	60.7	16/8	27.6	Post
Chan et al[42]	Taiwan/2012		4	26	52 (32 - 71)	24/2	25.2 (18.9 - 36.75)	Post
Gilat et al[43]	Israel/2013		4	15	57(27- 79)	5/10	24.1	Post
Teixeira et al[44]	Brazil/2013	Cross-sectional	4	14	64.9 (41- 84)	13/1	25.7 (19.4- 29.4)	Post
Faiz et al[24]	USA/2014		4	56	60 (28- 87) [b]	43/13	29 (12- 70.5)	Post
Zhu et al[45]	China/2014		4	9	48.1(33-74)	9/0	21.9(19- 24)	Pre
Huyett et al[46]	USA/2017		4	16	61.6 (48- 75) [b]	13/3	29.8 (22.7- 39.3)	Post
Loth et al[47]	France/2017		4	51	61.1 (44- 76)	37/14	23.2 (15.9- 33.7)	Post

Table 2: Summary characteristic of included studies (continued)

Study	Country/Year	Study Design	Level of Evidence	n	Age, Mean, (range),years	Male/ Female n/n	BMI, Mean (range), kg/m²	Measure at Pre/Post-cancer treatment
Saesen et al[48]	Belgium/2021		4	50	64.2 (32- 88) [b]	33/17	23.96 (17.51- 35.56) [b]	Post
Lin et al[49]	Taiwan/2014	Prospective	2	18	49.8	15/3	[Pre: 24.7, Post :21.8]	Pre and Post
Ouyang et al[50]	China/2019		2	40	(44-67)	37/3	[Pre:23. 3, Post:23. 6]	Pre and Post
Leone et al[51]	Italy/2020		2	6	58 (47- 70)	4/2	25.2 (23.4- 27)	Post
Huang et al[52]	Taiwan/2021		2	15	NA	14/1	56.2 (34-78)	Pre and Post
Huppert z et al[53]	Germany/ 2021		2	33 [Pre :33, Post: 17][a]	64 (46- 77) [b]	27/6	24.6 (15.8- 31.4)	Pre and Post
Santoso et al[54]	Netherlands/ 2019	Systematic review and meta-analysis	1	2315	24-87	1741/574	NA	Post/Pre and Post
Tawfik et al[29]	Japan/2021		1	268	39-71	206/62	25.6	Post/Pre and Post

[a]: The study has a different number of participants before and after treatment.

[b]: Median was used instead of mean

NA: Not assessed; BMI: Body Mass Index

3.4.2. The course of therapy for HNC patients with OSA

A summary of HNC treatment based on the cancer sites, cancer stages, and the treatment courses provided are presented in Figure 3. Among selected studies 14 studies[32,33,35-39,41-43,45,46,51,52] were included in this figure as they provided full treatment evidence. The total number of participants in the treatment review was 106 including oral and oral cavity cancer (68), pharyngeal cancer (22), laryngeal cancer (10), nasal cavity (1), unknown (1), and special cases (4). The observation suggested that the cancer site is the first concern in deciding treatment for HNC patients, then the cancer stage was considered to determine the adjuvant therapy and dose of treatment. Bedside, all studies suggested that chemotherapy was given concurrently with radiotherapy for patients with HNC rather than given only chemotherapy. In oral and oral cavity cancers (stage I-IV), it is shown that surgery was the most popular treatment. The commonly recommended surgery approaches in the literature review are composite resection (performed for an oral cavity oropharyngeal primary region), partial resection (resection in continuity with the maxilla), and hemi resection (surgery in continuity with mandibles). After primary surgery, three major reconstructive techniques were proposed including free flap (FF), pectoralis major myocutaneous (PMM), and split-thickness skin graft (STSG). Based on the cancer size and physical function of removed parts, patients will receive one of three reconstructive surgeries. In particular, adjuvant therapy by CRT and RT is also recommended for patients with the oral and oral cavity at stage II-IV. Unlike oral and oral cavity cancer, patients with pharyngeal cancer received surgery for early-stage and chemoradiotherapy and radiotherapy for stage II-VI. Same with pharyngeal cancer, chemoradiotherapy and radiotherapy were typically recommended for patients with laryngeal cancer at stage II-IV. In the remaining cases, patient with advanced cancer in the nasal septum was treated with chemoradiotherapy, radiotherapy was used for

patient with early-stage cancer in the lymph node, and for patients with tumors located in multiple sites (mouth and oropharynx). The common dose of radiation beam used in RT and CRT is 70 Gy, it may vary depending on tumor site and tumor size. Chemotherapy agents including cis-platinum (C) and Panitumumab (P) were suggested to use with 2 or 3 cycles at stage II and higher while stage I received only one cycle. Besides, the majority of OSA cases were reported in patients with three primary regions: oral and oral cavity, pharynx, and larynx. There was no evidence that suggested the difference in cancer treatment between OSA and non-OSA patients.
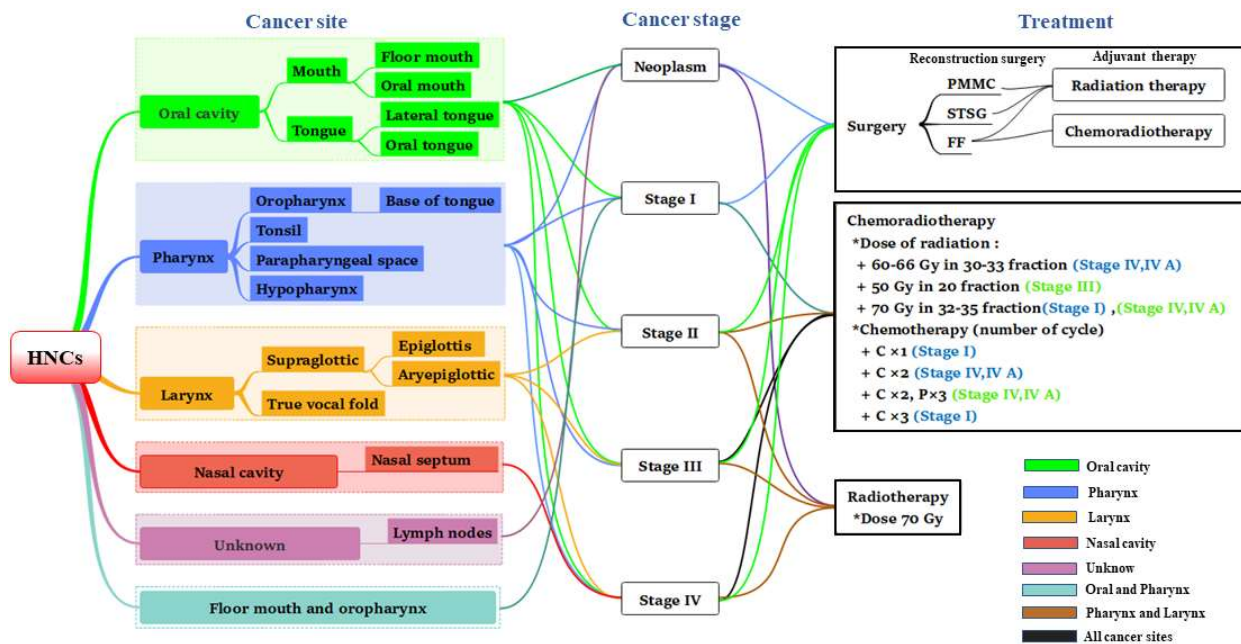
Figure 3: Summary of current treatment in HNC patients with OSA; PMMC: Pectoralis major myocutaneous, STSG: Split thickness skin graft; FF: Free flap; C: cis platinum; P: Panitumumab

3.4.3. The relationship between HNC and OSA

To answer the questions about the complex interaction between HNC and OSA, clinical data about HNC including tumor stage, tumor sites, tumor size, tumor stage, cancer treatment, its outcomes, and adverse effect were observed. Accordingly, causal relationships and non-causal relationships between OSA and HNC are reported. Figure 4 describes a summary of potential

relationships suggested by the research object of included studies as well as the mechanism that explained these interactions. In this section, to clarify the causal interaction and the association surrounding HNC and OSA, we divided into two main subsections to present the pieces of evidence corresponding to associate and causal relationships.
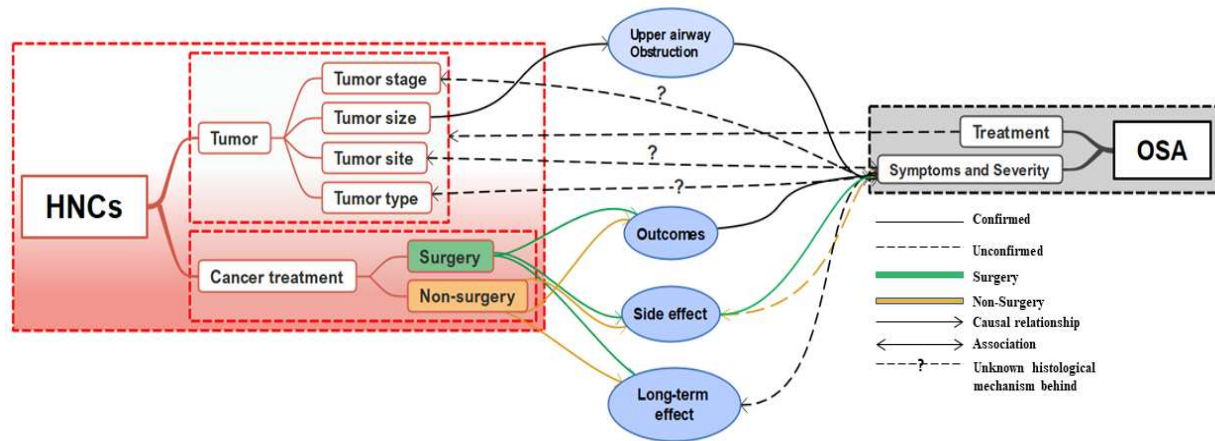
Figure 4: Summary the relationship between OSA and HNC

3.4.3.1. Association between HNC and OSA

Five main thematic features of HNC and OSA were extracted to determine the association including cancer site, cancer stage, cancer type, cancer treatment, and other outcomes of cancer therapy that are related to OSA. 14 studies were reviewed to clarify the association between HNC and OSA as shown in Error! Reference source not found.. In terms of diagnosis information of the tumor, there was no association between tumor site, tumor stage, or tumor type and OSA. Only one study observed that AHI has a positive correlation with primary cancer size[53].

There are two main groups of treatment: surgery (9)[24,41-44,47,48,50,53] and non-surgery (10)[24,35,36,41,46-49,51,53] includes CRT and RT. Among 10 studies of the surgery group, 3 studies describe a significant relationship between surgery and OSA [41,44,50]. One study suggested that surgery has more severe OSA than the non-surgery group (OR=5.5)[41]. In

addition, one other study concluded that OSA is more frequent in post-surgery than pre-surgery (Post:82 % and Pre:57%)[50]. Besides, OSA in patients treated with a vertical partial laryngectomy (VPL) and horizontal partial laryngectomy (HPL) has reported a conflict in the result. One study mentioned that OSA is more severe in patients treated with supracoracoideus partial laryngectomy (SCPL)-one type of HPL compared to VPL but the minimum SpO2 value of patients treated with SCPL is greater than VPL [50]. In contrast, one other study observed that OSA was worse with VPL than HPL and patients had a worse of minimum SpO2 after treating by VPL[44]. For the non-surgery group, 6 of 10 studies examined the relationship between OSA and these treatments[24,41,46-49]. Only 1 study reported that patients treated by RT were more suffering with OSA than non-RT (OR =11.47)[24] while other studies concluded there are no differences between treatment and non-treatment groups. In addition, one study described after being treated with CRT, the oxygen saturation in patients was significantly increased[49]. Besides OSA and treatment, other relationships between OSA or OSA relative factor and cancer characteristics was also evaluated. It was observed that BMI and age correlated with AHI[43,44]. Patients actively treated for cancer or less than 5 years from cancer diagnosis were more suffered from OSA[24].

Table 3: Summary of the association between HNC and OSA

Study/years	OSA (%)	AHI	Cancer treatment (n)	Association of OSA with cancer site	Association of OSA with cancer stage	Association of OSA with Cancer type	Association of OSA with cancer treatment	Other relationship/side effects
Ouyang et al [60]	Pre: 57, Post: 82	≥5	Surgery (40)	No relationship	NA	NA	AHI in SCPL higher than VPL	Min SpO2 value lower in VPL than SCPL
Faiz et al[29]	84	≥5, Mean :35	RT (44), Surgery (12)	NA	NA	No significant difference between SCC and no SCC	Patients treated by RT were more suffering with OSA than non-RT (OR =11.47)	Active cancer predicts the presence of OSA (OR=13)
Teixeira et al[54]	92.9	24.0	Surgery (14)	NA	NA	NA	AHI in VPL >HPL	Significant correlation between AHI and BMI VPL had a worse minimum of SpO2
Wei Qian et al[51]	95.8	Surgery: 27.96[a]; non-surgery: 15.9[a]	Surgery (15), CRT (9)	NA	No correlation	NA	+The surgery group had more severe OSA than the nonsurgical group	No relationship
Saesen et al[58]	40	NA	Surgery (31), RT (9), CRT (10)	NA	NA	NA	+No significant impact on the prevalence of OSA+ screening	No significant

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Table 3: Summary of the association between HNC and OSA (continued)

Study/years	OSA (%)	AHI	Cancer treatment (n)	Association of OSA with cancer site	Association of OSA with cancer stage	Association of OSA with Cancer type	Association of OSA with cancer treatment	Other relationship/side effects
Huyett et al[56]	50	13.9 (5.6-38.8) [b]	CRT (14), RT (2)	NA	No relationship	NA	No relationship	No relationship
Loth et al[57]	25.94	Surgery: 11.98±11.36 CRT: 10.62±15.12	CRT (41), Surgery (10)	No relationship	No relationship	NA	No difference between patients treated with CRT and Surgery	More fatigue in patients with OSA
Lin et al[59]	Pre: 72, Post: 78	Pre: 26.2, Post: 21.7	CRT (18)	NA	NA	NA	No significant difference before and after RT	Oxygen saturation significant increases after patients treated with CRT
Chan et al[52]	53.85	8.96	Surgery (25)	NA	No significant difference	NA	No significant difference	BMI was significantly greater in the OSA group
Huang et al[62]	100	Pre: 40.7, Post: 37.3	Surgery (15)				No significant difference	No significant change
Huppertz et al [63]	90	Post: 20.24, Pre: 20.49	RCT (12), Surgery (21)	NA	NA	NA	NA	Positive correlation between primary tumor size and AHI

Table 3: Summary of the association between HNC and OSA (continued)

Study/years	OSA (%)	AHI	Cancer treatment (n)	Association of OSA with cancer site	Association of OSA with cancer stage	Association of OSA with Cancer type	Association of OSA with cancer treatment	Other relationship/side effects
F.Leone et al[61]	100	Pre:44.5; Post: 3.8c	CRT (6)	NA	NA	NA	NA	NA
Gilat et al[53]	53	8±10.5	Surgery (15)	NA	No relationship	NA	NA	Age was positively associated with AHI

NA: Not assessed, RT: Radiotherapy, CRT: Chemoradiotherapy, BMI: Body Mass Index, VPL: vertical Partial Laryngectomy, HPL: Horizontal Partial Laryngectomy, SCC: Squamous Cell Carcinoma, SCPL: supracoracoideus partial laryngectomy

3.4.3.2. Potential causal relationship of HNC and OSA

In term of causal relationships of HNC and OSA , although there were no study were conduct to evaluate the causal effect of each condition to other, there were 8 case studies[32,35,37,39,45] that reported possible causal effects of HNC on OSA and OSA on HNC (Table 4). Five of them[32-34,38,45] mentioned the mass, malignant tumor in Head and Neck cancer regions that assessed by MRI, CT/PET caused obstruction in upper airway which leads to OSA in these patients. One study [48] observed a malignancy in tonsil from a patient with moderate OSA without underlying disease and risk factors for malignancy. Besides, a case of recurrence of cancer after 9 years caused OSA also mentioned [45]. After treated, these cases reported a significant improved of OSA. In contrast, 3 studies [35,37,39] suggested the presence of severe OSA after 2- 6 months treated with CRT and surgery. Moreover, one case study observed that after lingual and palatine tonsillectomy to treat OSA, patient was found to have squamous cell carcinoma in this region. In summary, mentioned studies suggest that HNC tumor and treatment may cause OSA and OSA surgery is one of potential reason making tumor arises in treated area. However, these observations can not provide a significant conclusion for causal relationship of HNC and OSA, more clinical experiments should be developed to measure them.

Table 4: Summary of evidence show potential causal relationship of OSA and HNC

Study/years	Causes of OSA	Causes of HNC	AHI, Pre, Post cancer treatment	Cancer treatment (n)	Influences of treatment:
Casale et al[42]	Parapharyngeal lipoma	NA	Pre: 65, Post: 31	Surgery	Reduce AHI and OSA symptom
Asai et al[43]	Tumor obstructing nasal cavity	NA	Pre:75.3, Post: 13	RT	+Reduce tumor size +Improved OSA symptom
Zhu et al[55]	Tumors in upper aerodigestive tract (parapharyngeal space, nasopharynx, oropharynx)	NA	Pre :41.2(15-80)	Surgery (4), CRT (5)	+OSAS related symptoms were absent after treatment +Tumor in parapharyngeal space treated by surgery was again and caused sudden breath apnea after 9 years
Kim et al[44]	Oropharyngeal mass	NA	Pre :58.7	Surgery	NA
Park et al[48]	Malignancy in tonsil	NA	Pre:21.4, Post:3.3	CRT	OSA was cured
Piccin et al[45]	Cancer treatment induced the severe OSA	NA	Post:49-55	Surgery (1), CRT (2)	+Severe OSA presences after 2-6 month of CRT
Pierre et al[47]	Cancer treatment	NA	Post:55	CRT	Developed Lhermitte's Sign and OSA symptom
Hoshal et al[49]	Severe OSA after cancer treatment	NA	Post:38	CRT	Presence of central sleep apnea and OSA
Courrtney et al [50]	NA	Lingual/palatine tonsillectomy for OSA	NA	CRT	NA

NA: Not assessed

3.4.4. Summary of statistical methods for the investigation of the association between Head and Neck cancer and OSA

This section outlines the statistical methods that have been used to address 3 main research questions regarding the association between HNC and OSA:

- What is the prevalence of OSA among HNC patients before and after cancer treatment? Are there any significant differences in OSA prevalence rates before and after treatment?

- Are there any significant differences in sleep-related parameters (e.g., ESS, AHI, RDI, min SpO_2, and sleep efficiency) in HNC patients before and after treatment?

- Are there any associations between HNC patient characteristics (e.g., demographics, BMI, living habits, and comorbidities) with sleep-related parameters, and between HNC-related factors (e.g., cancer site, size, stage, histology, pathology, oncologic therapy) with sleep-related parameters before and after treatment?

A growing body of literature has investigated the association between HNC and OSA with the focus on those three research questions. To answer these questions, most studies were designed to have the following measures: demographics (e.g., age, gender), clinical information (e.g., BMI, living habits, comorbidities), HNC-related variables (e.g., cancer site, tumor size, cancer stage), and sleep-related parameters (e.g., OSA severity, AHI, PSG, Epworth Sleepiness Scale (ESS) score, sleep questionnaires, Pulse Oximetry Oxygen Saturation (SpO_2), Respiratory Distress Index (RDI). As an important step in exploratory data analysis, the descriptive statistics of all variables are always computed in our 14 included cohort studies [24,41-44,46-50,52,53,55,56] to quantitatively summarize the measures obtained in the data sets.

Regarding the first research question, the prevalence rate of OSA before and/or after cancer treatment has been determined among HNC patients with different cancer sites, such as oral cavity and oropharynx [41,47,53,55], larynx [44], lateral tongue[42,43,53], multiple HNC locations [46,48], and hypopharynx[53], and treatments, such as surgical resection and reconstruction [41,42,55], chemoradiotherapy[41,47,53], radiotherapy[46,48,53], or surgery and chemoradiotherapy[47,53]. In these studies, the main statistical analysis was to use hypothesis testing and regression analysis. First, the OSA prevalence rate was estimated by calculating the proportion of patients with OSA before and after treatment. Consequently, statistical hypothesis testing was performed to validate if the mean difference in OSA-related parameters (e.g., AHI) or the proportion of patients with OSA are statistically different before and after the treatment. To confirm the difference in OSA-related parameters, paired t-test [41,53,55] were used to test the difference before and after treatment of the same cohort. Additionally, Chi-square test, Fisher's exact test, and non-parametric Mann-Whitney U test [42,46-48,53] were performed for comparing the continuous/categorical sleep measures of HNC patients' subpopulations (e.g., by age or gender) and general population with OSA. Binomial test has also been used to compare the proportion of patients with OSA after HNC treatment with the proportion of OSA in general population[48]. Recently, Santoso et al. [54] conducted a meta-analysis to investigate the prevalence of sleep disturbances including OSA among HNC patients before and after treatment. To our knowledge, this is the first systematic review and meta-analysis paper that combined the data and findings of the previous studies and analyzed the prevalence of OSA among HNC patients. The statistical methods used in this paper were meta-analysis methods and tests, such as Egger's regression test, Begg-Mazumdar's rank correlation test, and Duval-Tweedie's trim-fill test, which test for the potential publication bias and derive a pooled estimate closest to the

unknown ground truth based on the uncertainties reported in the previous studies. Here, mixed effects model was utilized to calculate the pooled prevalence rate of OSA under the assumption of heterogeneity in the study outcomes.

Next, the second research question has been addressed by 9 studies [32,33,36-38,49,50,52], in which 6 of them are case reports[32,33,35-38] describing cases at different rare primary sites (parapharyngeal space[32], nasal cavity and paranasal sinus [33,37], and tonsil [35,36,38]. In these case reports, simple descriptive analysis was conducted, which reports the measurement values and describe the difference in the values of the sleep measures before and after treatment without performing any statistical inference or hypothesis testing. The remaining 3 studies [49,50,52] mainly used statistical hypothesis testing to determine if there are any significant differences in sleep-related parameters in HNC patients when receiving the cancer treatment. In these studies, more common primary sites have been considered, which includes nasopharynx [49], larynx[50], and oral cavity or oropharynx[52]. Nasopharyngeal, oral cavity or oropharyngeal cancer are treated by a therapy course consisting of radiotherapy, chemotherapy, and surgery; however, the primary treatment of laryngeal carcinoma is partial laryngectomy [50]. The significance of the differences in the sleep-related parameters before and after applying these treatments was validated using paired t-test [50,52], Fisher's exact test [49], and Wilcoxon signed rank test[49].

Lastly, the most important research question that are concerned with the association between the sleep-related measures and other relevant factors among HNC patients has been answered by many cohort studies[24,41,43-48,50,51,53,56]. In the study conducted by Zhu et al [45] the causal association between a rarely reported tumor, namely upper aerodigestive tract tumor, and OSA, has been studied. Leone et al [51] examined OSA as a sequela of non-surgical treatments of selected HNN cancer and documented dynamic anatomical and functional

alterations during sleep in irradiated OSA patients by drug-induced sleep endoscopy. Both studies described cases in their papers thoroughly using descriptive analysis and showed consistent evidence that there exist potential causal associations between OSA and cancer treatments. However, there has been no hypothesis testing being performed because of the small sample sizes. With larger sample sizes, the other studies [24,36,41,43,44,46-48,50,53,56] have attempted to implement different hypothesis testing or correlation analysis to investigate the associations between patient demographics (e.g., age, sex, BMI, comorbidities) versus OSA severity (indicated by AHI or Respiratory Distress Index (RDI))[24,41,43,44,46-48,53,56], between Epworth Sleepiness Scale (ESS), sleep-related questionnaire score, and min SpO2 versus OSA severity[41,43,44,46,47,53], between treatments versus OSA severity and ESS [24,41,46,47,50,56], between treatments versus patient characteristics[24,41,44,47,48,50], and between tumor characteristics (e.g., stage, site, size, and tumor-related mortality) versus OSA severity [24,41,43,46,47,53]. The hypothesis tests used for determining of the significance of association were Chi-square test [56], Fisher's exact test[24,43,46-48,56], student t-test[41,56], Mann-Whitney U test [43,44,46,48,56], Wilcoxson rank-sum test [24], and two-way repeated measures multivariate ANOVA [60]. The strength of the linear association between two variables was mainly estimated by Pearson correlation coefficient [51,57,63] and Spearman's rank correlation coefficient [43,44]. There were only 3 papers[24,29,53] that applied statistical modeling for analyzing the relationships between independent variables (e.g., clinical variables) and dependent variables (e.g., OSA severity) in their statistical analysis. In the first paper authored by Faiz et al [24], multivariate logistic model has been utilized to examine the relationship between OSA and patient characteristics. The next paper[11] applied mixed-effects model to investigate the influence of fixed factors as tumor site and stage and random effects (age, BMI, neck

circumference, tumor size, and AHI) on sleep-related parameters. The last paper was a meta-analysis study published recently in 2021, which studied the association of OSA with radiotherapy using mixed-effects model [56]. The assumptions and limitations of all statistical methods being used to address those three research questions were summarized in Table 5. The details of the statistical analysis approaches that have been applied in the studies investigating about the association HNC and OSA were illustrated in Table 6. In this table, we also included two extra papers[55,56] published before 2010 because of the relevance of their statistical analysis approach.

Table 5: Summary of assumptions and limitations of the applied statistical methods

Research questions	Statistical methods	Assumptions and restrictions
1. What is the prevalence of OSA among HNC patients before and after cancer treatment? Are there any significant differences in OSA prevalence rates before and after treatment?[41-44,46-48,53,54]	Descriptive statistics	Cannot infer about the properties/parameters of a population
	Paired t-test	SI, NA for the distribution of differences, RS
	Chi-square test	Variables are categorical, SI, observations are ME, $E[cells] \geq 5$ in $\geq 80\%$ of cells
	Fisher's exact test	RS, SI, observations are ME, $E[cells] < 5$ in $\geq 20\%$ of cells
	Mann-Whitney U test	SI, 1 continuous/ordinal DV and 1 dichotomous IV, sensitive to the difference in the distributions of the two groups of the IV
	Meta-analysis methods	Selected from primary studies not from a RS, subject to high publication bias, heterogeneity, low-quality studies, small-study effect [57]
	Mixed-effects model	LA, no outliers, homoscedasticity, NA of Residuals, no multicollinearity [58]
2. Are there any significant differences in sleep-related parameters in HNC patients before and after treatment?[32,33,35-38,49,50,52]	Descriptive statistics	LA, no outliers, homoscedasticity, NA of Residuals, no multicollinearity
	Wilcoxon signed-rank test	The population distribution of the difference scores is symmetric, RS of difference scores, SI, continuous/ordinal DV
	Fisher's exact test	The population distribution of the difference scores is symmetric, RS of difference scores, SI, continuous/ordinal DV
	Paired t-test	The population distribution of the difference scores is symmetric, RS of difference scores, SI, continuous/ordinal DV

Table 5: Summary of assumptions and limitations of the applied statistical methods (continued)

Research questions	Statistical methods	Assumptions and restrictions
	Descriptive statistics	The population distribution of the difference scores is symmetric, RS of difference scores, SI, continuous/ordinal DV
	Chi-square test	The population distribution of the difference scores is symmetric, RS of difference scores, SI, continuous/ordinal DV
	Fisher's exact test	The population distribution of the difference scores is symmetric, RS of difference scores, SI, continuous/ordinal DV
	One-sample t-test	SI, NA of data, homogeneity of variances, RS
3. Are there any associations between HNC patient characteristics with sleep-related parameters, and between HNC-related factors with sleep-related parameters before and after treatment?[24,29,41,43-48,50,51,53]	Mann-Whitney U test	The population distribution of the difference scores is symmetric, RS of difference scores, SI, continuous/ordinal DV
	Two-way repeated measures multivariate ANOVA	Continuous DV, 2 IV consist at ≥ 2 categories, no significant outliners, NA of DVs, sphericity (equal variances of the differences between all combinations of related groups)
	Pearson correlation	SI, RS, LA, handle 2 continuous variables, NA of data, no outliers
	Spearman's rank correlation	SI, RS, LA, handle 2 continuous/ ordinal variables, NA of data, no outliers
	Multivariate logistic model	SI, RS, binary DV, LA of IVs and log odds, no multicollinearity, large sample size
	Meta-analysis methods	SI, RS, binary DV, LA of IVs and log odds, no multicollinearity, large sample size
	Mixed -effects model	SI, RS, binary DV, LA of IVs and log odds, no multicollinearity, large sample size

SI: Subject Independence, RS: Random sampling, NA: Normality Assumption, ME: Mutually Exclusive, $E[\cdot]$: expected value, DV: dependent variable, IV: independent variable, MA: Mentioned above, ANOVA: Analysis of variance, LA: Linearity Assumption

Table 6: Summary of statistical analysis approaches

Statistical analysis approach	Study/Year	Patient measures	Statistical methods	Objective	Limitations
Approach 1: Descriptive analysis	Casale et al[32]/2012	Cervical MRI, AHI and ESS	Descriptive statistics: + Report AHI and ESS before and after the treatment + Percentage	Describe parapharyngeal lipoma in an obese adult patient under transcervical surgery that causes anatomic pharyngeal obstruction with OSA	
	Asai et al[33]/2013	HNN-MRI, ESS, BMI, BP, SpO$_2$, AHI and tumor size	Descriptive statistics: + Report ESS, BMI, BP, SpO$_2$, AHI and tumor size before and after the treatment	Describe an obese woman with OSA syndrome caused by malignant melanoma in the nasal cavity and paranasal sinus, which was treated by irradiation	+ Only report limited cases + No statistical inference or hypothesis testing
	Zhu et al[45]/2014	Gender, Age, BMI, Cancer site, tumor size, pathology, treatment, follow-up time, PSG data, MRI & PET/CT, SpO$_2$, and AHI	+ Descriptive statistics: gender, age, BMI, AHI, treatment therapy, pathology, and cancer site	Reported OSA caused by 9 cases of preoperative uncommon upper ADTT including nasopharyngeal SCC, oropharyngeal SCC, hypopharyngeal SCC and laryngeal SCC.	
	Piccin et al[35]/2016	BMI, ESS, AHI, ODI, and SpO$_2$	Descriptive statistics: + Report AHI, ODI, and SpO$_2$ before and after the treatment	Describe 2 cases of severe OSA induced by neck surgery and radiotherapy treated with an oral device	
	Zheng et al[59]/2017	BMI, AHI, RDI, ESS, HPV test, treatment, cancer site and stage, and SpO$_2$	Descriptive statistics: + Report AHI, ESS, RDI, and SpO$_2$ before and after the treatment	Present a case of hypoglossal nerve upper airway stimulator implantation for OSA in a patient who underwent prior radio-chemotherapy for tonsillar carcinoma	

Table 6: Summary of statistical analysis approaches (continued)

Statistical analysis approach	Study/Year	Patient measures	Statistical methods	Objective	Limitations
Approach 1: Descriptive analysis	Pierre et al[37]/2018	BMI, cancer drug doses, AHI, and SpO$_2$	Descriptive statistics: + Report AHI and SpO$_2$ before and after the treatment	Describe a case of locally advanced HNN squamous cell carcinoma treated with chemo followed by CRT and developed a post treatment occurrence of OSA	
	Park et al[38]/2020	RDI, cancer therapy doses,	Descriptive statistics: + Report RDI before and after the treatment	Describe a case of a 59-year-old man who experienced unexpected occult malignancy diagnosed during tonsillectomy surgery for OSA and was treated by chemotherapy and radiotherapy	
	Leone et al[51]/2020	Gender, age, histology, cancer site and stage, treatment, time between RT and OSA, BMI, AHI, DISE, follow-up time, medical images, PSG data, vNRS-11 and I-EAT 10 questionnaire	+ Descriptive statistics of all variables	Focus attention on OSA as a sequela of non-surgical treatments of selected HNN cancer and document dynamic anatomical and functional alterations during sleep in irradiated OSA patients by drug-induced sleep endoscopy (DISE)	

Statistical analysis approach	Study/Year	Patient measures	Statistical methods	Objective	Limitations
Approach 2: Approach 1 + correlation analysis + hypothesis testing	Qian et al[41]/2010	Gender, age, tumor site, TNM staging, flap size, RDI, treatment, ESS, BMI, and min SpO$_2$	+ Descriptive statistics of all variables + Pearson correlation: RDI & (BMI, ESS, SpO$_2$, and TNM) + t-test: compare mean difference in RDI between genders and age groups	Determine the prevalence of OSA in patients following oral and oropharyngeal cancer treatment Test the correlation between RDI & (BMI, ESS, SpO2, and TNM); compare patients between surgical and nonsurgical groups; compare mean difference in RDI between genders and age groups	+ Small sample size + Incomplete matching on primary site, BMI, and thyroid function + Low sensitivity of ESS
	Chan et al[42]/2012	Gender, age, BMI, min SpO$_2$, AHI, tumor size, glossectomy, neck dissection, reconstruction, radiotherapy	+ Descriptive statistics of all variables + Chi-square and Fisher exact test: compare the test results of tongue-cancer patients with OSA and general population with OSA	Determine the prevalence of OSA in patients with squamous cell carcinoma of the tongue following ablation surgery	+ Small sample size + Incomplete matching on age, snoring index, tumor size, local recurrence, neck lymph node metastasis, neck dissection, and radiotherapy

Table 6: Summary of statistical analysis approaches (continued)

Statistical analysis approach	Study/Year	Patient measures	Statistical methods	Objective	Limitations
Approach 2: Approach 1 + correlation analysis + hypothesis testing	Gilat et al[43]/2013	Gender, age, smoking habits, BMI, medical history, tumor site and stage, oncologic therapy, % tongue resected, flap size, degree of OSA, ESS, PSG data, and AHI	+ Descriptive statistics of all variables + Binomial test: compare the rate of OSA between the cancer patients and the general population + Nonparametric Mann-Whitney test: compare AHI between two populations by patient sex and age; compare patients with and w/o OSA for age and BMI + Spearman's correlation: AHI & (Age, BMI, ESS, tumor T stage) + Fisher's exact test: test the association between sex and age with AHI	Compare the rate of OSA between the cancer patients and the general population Determine if radial forearm free flap reconstruction of the tongue after partial glossectomy is associated with OSA	+ Overlooked cofactors such as tiredness and weariness + Low sensitivity of ESS
	Teixeira et al[44]/2014	Gender, age, BMI, neck circumference, Tumor stage, cancer therapy, PSG data, ESS, AHI, min SpO_2, and spirometry data	+ Descriptive statistics of all variables + Mann-Whitney U test: compare between PHL and PVL groups + Spearman's rank correlation: AHI & other variables	Compare the prevalence and severity of OSA in patients submitted to PHL and PVL Compare variables between PHL and PVL groups	+ Small sample size + Unvalidated causal inference + Selection bias + Insufficient matching on age and smoking habits

Table 6: Summary of statistical analysis approaches (continued)

Statistical analysis approach	Study/Year	Patient measures	Statistical methods	Objective	Limitations
Approach 2: Approach 1 + correlation analysis + hypothesis testing	Lin et al[49]/2014	Gender, age, cancer treatment, PSG data, ESS, subjective SRBD symptoms, min SpO2, sleep stage, and AHI	+ Descriptive statistics of all variables + Wilcoxon signed rank & Fisher's exact test: compare pre-treatment and post-treatment data	Clarify the impact of HNN radiotherapy on SRBDs and investigate the change of sleep architecture in patients with NPC before and after treatment	+ Lack of control group + Small sample size + Selection bias + ESS may lack sensitivity + Potential confounders: variability in the regimens of cancer therapy + Complication of RT and CRT
	Huyett et al[46]/2017	Gender, age, BMI, smoking status, comorbidities, cancer stage, HPV, time from RT, AHI, min SpO$_2$, cancer therapy, ESS, UWQOL, FOSQ-10, and T90	+ Descriptive statistics of all variables + Independent-samples Mann-Whitney U test: compare continuous variables + Fisher's exact test: compare categorical variables	Assess the prevalence of OSA in HNN cancer patients treated with radiation therapy Compare the differences in age, BMI, dose, tumor primary site or stage, HPV status, Self-reported questionnaire scores, or comorbidity status between the OSA and non-OSA groups.	+ Inconsistent reported prevalence of OSA in the general population + PSG was not recorded + Selection bias

Table 6: Summary of statistical analysis approaches (continued)

Statistical analysis approach	Study/Year	Patient measures	Statistical methods	Objective	Limitations
Approach 2: Approach 1 + correlation analysis + hypothesis testing	Loth et al[47]/2017	Gender, age, BMI, comorbidities, treatments, alcohol and tobacco consumption, cancer history, sleep history, physical examination, ESS, EORTC QLQ-C30 and EORTC H&N35 questionnaires, blood test, PSG data, and AHI	+ Descriptive statistics of all variables + Fisher's exact test: compare categorical variables + Pearson correlation: ESS & PSG data, questionnaire answers & OSA	Evaluate the prevalence of OSA in a population of patients treated for an advanced oropharyngeal cancer (AJCC Stage III or IV) Compare the difference between patients treated with either surgery or CRT; compare the difference in EORTC QLQ C-30 questionnaire score between OSA and non-OSA groups	+ Small sample size + Unaccounted factors that contribute to the increased incidence of OSA + Selection bias
	Ouyang et al[50]/2019	Gender, age, BMI, PSG data, AHI, cancer stage, min SpO$_2$, ESS, CT image, MRI, and surgical method	+ Descriptive statistics of all variables + Paired student's t test: compare quantitative data + Two-way repeated measures multivariate ANOVA: compare the SCPL and VPL groups	Investigate whether partial laryngectomy is a risk factor for OSA and the effect of different partial laryngectomy methods on OSA after treatment Compare the differences in AHI and min SpO$_2$ between the SCPL and VPL groups	Not mentioned

Table 6: Summary of statistical analysis approaches (continued)

Statistical analysis approach	Study/Year	Patient measures	Statistical methods	Objective	Limitations
Approach 2: Approach 1 + correlation analysis + hypothesis testing	Saesen et al[48]/2021	Demographics, BMI, medication uses, living habits, ESS, Berlin questionnaire, PHQ-9 questionnaire, and CIS-20 questionnaire	+ Descriptive statistics of all variables + Binominal test: compare the proportion of patients with OSA after RT with that in the general population + Fishers exact test & Mann Whitney U test: examine risk factors for developing OSA after RT	Confirm if OSA is more prevalent after receiving RT for HNC Investigate the risk factors for developing OSA in this population	+ Small sample size + Lack of control group + Selection bias
	Huang et al[52]/2021	Gender, age, tumor site, cancer stage, pathology, surgery treatment, defect size, free-flap size, free flap, SpO_2, PSG data, AHI, heart rate, Postop PSG, and postop $\triangle$mHR	+ Descriptive statistics of all variables + Paired t-test: examine the changes against no change after the surgery	Compare the PSG data before and after the surgery in patients with oral cavity or oropharyngeal cancers without a chemo- or radiotherapy.	+ Small sample size + Selection bias
Approach 3: Approach 1 & 2 + regression analysis	Faiz et al[24]/2014	Gender, age, BMI, comorbidities, cancer pathology, primary cancer site, disease status, treatment, sleep history, AHI, sleep stage, sleep efficiency, SpO_2, ESS, and PSQI	+ Descriptive statistics of all variables + Fisher's exact test: compare groups for categorical variables + Wilcoxon rank-sum test for continuous variables + Multivariate logistic model: examine the relationship between OSA and patient characteristics	Describe the characteristics of sleep disorders in patients with tumors located in the HNN region based on PSG data and to determine the risk factors and symptoms of OSA in these patients.	+ Selection bias + Potential confounders coexisting sleep disturbances

Table 6: Summary of statistical analysis approaches (continued)

Statistical analysis approach	Study/Year	Patient measures	Statistical methods	Objective	Limitations
Approach 3: Approach 1 & 2 + regression analysis	Huppertz et al[53]/2021	Gender, age, BMI, neck circumference, comorbidities, cancer history, treatment, cancer site and stage, tumor size, living habits, AHI, SpO₂, ESS, PSQI, ISI, EORTC QLQ-C30 and SF 36 questionnaire	+ Descriptive statistics of all variables + Mixed effects model: investigate the influence of fixed factors (tumor site and stage) and random effects (age, BMI, neck circumference, tumor size, and AHI) on sleep-related parameters + Paired t-test: examine the change difference in pre-treatment and post-treatment + Pearson correlation analysis: examine the correlation between fixed and random factors and sleep-related parameters	Evaluate the prevalence of OSA and its impact on the quality of life in patients with oropharyngeal, hypopharyngeal and lateral tongue squamous cell carcinoma of the HNN Investigate the association between tumor-related factors and other random effects with sleep-related parameters.	+ Small sample size + Selection bias + Limited statistical power of the observations after treatment

Table 6: Summary of statistical analysis approaches (continued)

Statistical analysis approach	Study/Year	Patient measures	Statistical methods	Objective	Limitations
Approach 4: Meta-analysis	Santoso et al [54]/2019	Data were collected from relevant studies investigating the prevalence of OSA among HNN cancer patients	+ Mixed-effects model: calculate the pooled prevalence rate of OSA[54]; Investigate association between OSA and radiotherapy [29] + Inconsistency measure (I^2): assess heterogeneity among studies + Funnel plots and: examine the publication bias	Investigate the prevalence rates of various types of sleep disturbances among HNN cancer patients before, during, and after cancer treatment	+ Considerable heterogeneity + Limited number of studies with small sample size, which hinders the power of statistical methods + Lack of longitudinal studies
	Tawfik et al[29]/2021	Data were collected from relevant studies investigating the association between OSA and RT	+ Egger's regression test and Begg-Mazumdar's rank correlation test: test the presence of publication bias + Duval-Tweedie's trim-fill test: calculate the adjusted pooled estimates	Investigate association between OSA and radiotherapy in HNN cancer patients	+ Publication bias + Non-validated instruments were used to measure OSA

OSA: Obstructive Sleep Apnea, MRI: Magnetic Resonance Image, AHI: Apnea Hypopnea Index, ESS: Epworth Sleepiness Scale, HNN: Head and Neck, BMI: Body Mass Index, BP: Blood Pressure, SpO2: Pulse Oximetry Oxygen Saturation, ODI: Oxygen Desaturation Index, RDI: Respiratory Distress Index, TNM: tumor (T), node (N), and metastasis (M), PSG: Polysomnography, w/o: Without, PHL: partial horizontal laryngectomy, PVL: partial vertical laryngectomy, PSQI: Pittsburgh Sleep Quality Index, ADTT: upper aerodigestive tract tumor, SCC: squamous cell carcinoma, PET/CT: Positron Emission Tomography - Computed Tomography, FOSQ = Functional Outcomes in Sleep Questionnaire, T90 = Time spent below 90% O2 saturation; UW QOL = University of Washington Quality of Life, HPV = Human Papilloma Virus, RT = Radiation Therapy, CRT: Chemoradiotherapy, PHQ: Patient Health Questionnaire, CIS: Checklist Individual Strength, SRBDs: Sleep-related Breathing Disorders, NPC: Nasopharyngeal Carcinoma, SCPL: Supracricoid Partial Laryngectomy, VPL: Vertical Partial Laryngectomy, vNRS-11: Verbal Numerical Rating Scale 11, I-EAT-10: Eating Assessment Tool 10 (Italian version), Postop PSG: Days a postoperative polysomnography was done after the surgery; Postop △mHR: Postoperative mean heart rate change (beats/minute), ISI: Insomnia Severity Index

3.5. Discussion

3.5.1. Treatment for patients with HNC

The guide of treatment was specified by the site of cancer, stage, and pathologic findings. Generally, RT or surgery is recommended for 30-40% of patients with early stage of cancer (stage I or II)[21]. In this study, at early stages, single treatment was provided such as surgery typically treated patients with oral cavity and primary oropharyngeal while patients with other cancer sites were treated by CRT and RT. For the advanced stage of cancer, single treatment was instead of combined therapy. Accordingly, the aforementioned studies also describe that adjuvant therapy will be provided after surgery for patients who present the advantage stage of HNC. In addition, the number of patients who received CRT was also higher than the RT patient because most of the patient was examined in these studies presenting at stage III and IV. As mentioned, cancer stages may have a relationship with OSA but in these studies, the participant with early cancer stages has a small size compared to advantaged stages. Hence, it is a challenge to evaluate the effect of the cancer stage with OSA. In HNC patients with OSA, it reported that no case was treated by new approaches such as targeted therapy, gene therapy, or immunotherapy. It happens due to the limitation about the understanding of histological and clinical trials for HNC are still ongoing research.

3.5.2. Relationship between the biology of cancer and OSA

As mentioned, the lack of histological and molecular evidence about Head and Neck cancer with OSA is one most of the challenges to developing a new therapy for HNC patients with OSA as well as determining the pathophysiological mechanism between HNC and OSA. Currently, only some pieces of evidence have been observed that describe the relationship between OSA and the biology of cancer. Epidemiological studies demonstrated OSA is a risk

factor for cancer. Accordingly, it suggested 2 major hallmark features of OSA: intermittent hypoxia (IH) and sleep fragmentation (SF) which may have influences on outcomes of cancer (Figure 5). In particular, there are several suggested mechanisms by which SF and IH may affect tumor biology. To mimic OSA, rapidly cyclical hypoxia was set up by active or inhibiting a certain pathway. One of the key mechanisms in response to IH is known as the hypoxia-induced factor (HIF). HIF is made up by HIFα and HIFβ that orchestrates the transcription of at least 2500 genes to allow cells to adapt to situations of tissue hypoxia[62]. When HIFα can active the production of vascular endothelial growth factor (VEGF) that involved in angiogenesis by forming new blood vessels to supply more oxygen for tumors and avoid areas with a vascular obstruction[62]. Besides, activation of HIF in tumors is also associated with increased tumor cell survival, resistance to chemotherapy, radiotherapy that leads to a poor prognosis in cancer patients [63,64]. In addition, other transcription factors activation also leads to the presence of systemic inflammatory and oxidative stress responses. Oxidative stress can induce DNA oxidation and combine with inflammation by sleep apnea profiles to cause the mutation or accelerate the malignant transformation[65-67].In the animal model, IH events from moderate to severe OSA were mimicked to examine the role of IH in tumor growth[68]. Consequently, it reported the increase of malignant characteristics such as proliferation, migration, and invasion in melanoma, lung, prostate, and breast cancer. In addition, in a group of mice exposed IH, it reported the presence of T cell (Tregs)-immune suppressor[69]. Tregs can promote the development of tumor progression and metastasis. There is some evidence was associated with the shift in tumor macrophage M2 which was evaluated via the characterized of Tumor-associated macrophages (TAMs) protein membrane [12,70]. When macrophages presented a shift toward M2 polarization, it observed the inducing of tumor cell proliferation, migration, and

invasion of the tumor. Same animal model design as IH, SF was observed that disrupted sleep in

OSA accelerated TC1 and 3LL tumor progression [12,71]. Moreover, both IH and SF were

suggested that directly associated with the increase of sympathetic outflow which causes the

imbalance of the autonomic nervous system. In summary, the animal model of OSA suggested

that it induced the downregulation of immune response, accelerated tumor growth, and increase

the malignant transformation. Currently, the relationship between OSA and HNC was not

explored at the histological level. Only some studies evaluated the average oxygen level in HNC

tumors[72]and the relationship between hypoxia marker with SCC or the influence of hypoxia

with radiotherapy in HNC [73].
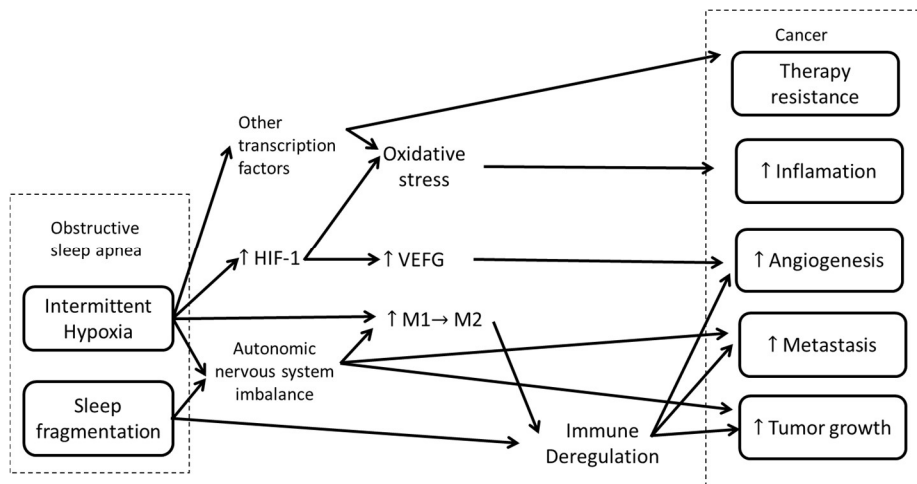
Figure 5: Summary of relationship between OSA and biology of cancer

3.5.3. The relationship between HNC and OSA

Tumors in Head and Neck cancer regions can develop OSA, however, in some cases the

tumors only found when patients failed in treating OSA. The reasons were that the neoplasms

that begin in unexpected location or rare such as parapharyngeal space and these cases typically

are difficult for early diagnosis if patients did not report any symptoms. Therefore, it suggested

that upper airways scan was necessary for OSA patients to decide the treatment as well as

improve the survival rate in case of patients with HNC. Besides, there was no evidence to determine whether OSA promotes the develop of malignant in patients with HNC. Only one study reported that an unexpected of malignant tumor was diagnosis in OSA patients without risk factor for malignancy[48].

Accordingly, there were some mechanisms that supported the relationship between HNC treatment and OSA (Figure 4). To explore the causes behind the relationship between OSA and HNC surgery, it was conducted CT scans and MRI to observe the change in the target organ. There are several reasonable explanations for the association between HNC surgery and OSA. First, it caused the thickening of the arytenoid mucosa that leads to stenosis of the airway inlet. Second, in the SCPL group, thyroid cartilage was removed while a unilateral resection was conducted in the VPL group, and then it was replaced by soft tissue[44,50]. Typically, thyroid cartilage of the bony works as a support tissue of the laryngeal cavity and avoids the collapse of tissue. However, the results from image approaches describe that the replaced soft tissue is not able to support the laryngeal cavity and the tissue is easier to collapse during inhalation. Same as oral cavity patients, the replaced tissue cannot provide the mechanical functions as a normal tongue that affects the working of relative muscles in the upper airway. Besides, the displacement of the tongue can reduce the posterior airway space that is negatively correlated with the severity of OSA[74].

About the association between OSA and non-surgery treatment (RT and CRT), it was first suggested by Friedman et al[75], that the frequency of OSA was higher in the RT group. Accordingly, there are several studies have evaluated this relationship but only 1 study has provided sufficient evidence to support this association[24]. Some possible mechanisms support the assumption about the occurrence of OSA in patients with HNC undergoing RT related to the

long-term and late effects of radiation[76]. First, the common effect after treating by radiation is xerostomia (dry mouth) and oral infection that damaged the upper airway structures as well as its normal function[77,78]. Besides, radiation caused dysphagia that happened by the reduction of elastic and increasing of fibrosis in the oropharynx[78]. The development of dysphagia may cause poor pharyngeal constriction, reducing the strength and retraction of the tongue base, and may damage the skeletal muscles[79,80]. Salivary gland dysfunction with reduced production of mucins may increase salivary viscosity and resistance of the airway[24]. In addition, radiation also causes hypothyroidism which is accelerated the progression of chronic edema[78]. One more late effect of radiotherapy is injuring the lower cranial nerves, which leads to abnormal function of pharyngeal muscles[80].

In terms of other relationships, about 10 years, no studies provide any evidence that suggested the relationship between cancer stage and OSA even one study proposed an association between OSA and tumor stage in 2006[81]. Only one article can observe the positive correlation between AHI and tumor size while others reported insignificant findings[53]. BMI, age, sex, fatigue could be confounders between HNC and OSA. Two studies suggested BMI[42] and age[43] were significantly greater in the OSA group and one suggested more fatigue [47] in patients having OSA. In summary, there are several limitations such as small sample size, insufficient statistic power to provide hypothesis testing and most studies collecting data after patients received treatment, and lack of information about baseline information.

3.5.4. Study design, statistical method, and confounders

In terms of experimental design, all the included studies were observational due to the scarcity of HNC cases at different primary tumor sites and cancer treatments, in which researchers can only observe the effect of risk factors, cancer treatments, or OSA interventions

without modifying those factors. Particularly, their study design was either cross-sectional (retrospective) cohort studies[24,41-48,55,56] or prospective (longitudinal) cohort studies [49-53]. The selection of study design is highly dependent on the main research questions (e.g., cross-sectional study designs are useful when researchers want to answer questions about the prevalence of OSA among HNC patients and prospective studies investigate the development of OSA before and after cancer treatments and relate this to other risk or protection factors). Other factors that influence the study design are budget, time, patient feasibility and research expertise. Therefore, experimental studies, such as randomized control trials (RCTs), are highly desired for producing reliable evidence but are impractical since they require a huge amount of resources and are unethical (e.g., randomizing cancer treatments) [82,83]. Despite that cross-sectional cohort studies are not expensive, less time-consuming, and allow to collect data from a large pool of subjects, they cannot determine cause-and-effect relationships and analyze the characteristics of the cohort over a period. On the other hand, prospective cohort studies have clarity of temporal sequence of exposures and outcomes and facilitate the study of rare exposures (e.g., hormone therapy or targeted drug therapy), but a large number of subjects are required to follow-up for a long time period, which makes the study design impractical and expensive for rare diseases or diseases with a long latency. In addition, the results of observational studies are subject to the risk of confounding effects and selection bias[84]. All studies we considered in this review paper selected the sample size according to the availability of HNC patients except for only 1 paper [48] that mentioned about the sample size determination using a theory-based formula based on the power of the one-sided Chi-square test at 80% with significance level of 0.05. Therefore, when sufficient resources and funding are available, more prospective (longitudinal) cohort studies should be conducted with adequate control for potential confounding factors, theory-based

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selection of sample size, longer follow-up time, and more time points (e.g., before treatment, during treatment, 6 months/1 year/2 years after treatment).

Regarding the statistical analyses used in the included studies, all the studies calculated descriptive statistics of all variables of intertest, but the descriptive statistics cannot make determinations about the characteristics of different populations or compare the statistical differences between multiple groups in the population. Hence, statistical hypothesis testing and correlation analysis have been extensively applied in many studies to answer three main research questions posed in Section IV.4 that are related to HNC and OSA. However, the conclusions from hypothesis tests do not explain the reasons that cause the significance of the differences between groups and cannot be expressed with full certainty. Similarly, correlation analysis also has its own limitations such as the assumption of linearity, the sensitivity to the range of observations, and more importantly the non-causality of correlation. Hence, to control for potential confounding factors and quantify the effects of other relevant risk/protection factors on outcomes of interest (e.g., AHI), regression analysis has been only used in 4 papers [24,29,53,54], for estimating the relationships between a dependent variable and a set of independent variables. The obtained statistical model can be used for prediction and forecasting, which has some overlap with machine learning field. Moreover, regression analysis can sometimes be utilized to infer causal relationships between the independent and dependent variables if temporal orderings of variables are known and a complete matching on confounders are achieved. Meta-analysis has been conducted in 2 papers [29,54], which combined the data and findings of the previous studies and constructed mixed-effects models to investigate the relationships between HNC-related factors and patient characteristics with OSA measures. In our opinion, researchers are encouraged to perform statistical modeling and apply more machine learning tools into the

papers to better understand the underlying relationships among the variables and explain the mechanisms causing the differences between different groups in the population. If possible, causal inference [83] or longitudinal causal inference techniques [85] can be employed to better determine cause-and-effect relationships of interest.

Regarding confounding variables, both confirmed and potential confounders have been mentioned in many papers [24,41,42,44,47,49,56], which are primary site [41], BMI [41,47], thyroid function[41], depression during postoperative period[56], age[42,45,47], snoring index [42,47], tumor size[42], local recurrence [42], neck lymph node metastasis[42], neck dissection[42], variability in the regimens of cancer therapy [42,49], smoking habit [44], and other coexisting sleep disturbances[24]. Confounding effects arise naturally in observational studies where the sample selection is based on non-random sampling without treatment randomization. Therefore, controlling for confounders is extremely important to determine cause-and-effect relationships. In the literature, there are many techniques to maximally reduce the confounding effects, namely adding all control variables along with the independent variable as predictors in regression analysis, stratification, matching, and statistical "correction" or "re-weighting" [85]

3.6. Conclusion

The current review suggests a complex interaction between HNC surgery and OSA including association and causation. In particular, the observations from cross-sectional and prospective studies suggest that cancer treatment and tumor size associate with OSA the change of AHI while the evidence from case studies illustrate that HNC tumor cause OSA and OSA surgery led to the presence of HNC tumor in resection region. In term of statistical analysis, descriptive statistics, hypothesis testing and regression model were the most common methods used to determine the relationship between OSA and HNC. In addition, there are no longitudinal

study that measure the change of HNC patients with OSA during the time of cancer treatment while this type of study can provide valuable information how HNC and OSA interact and suggest more effective statistical method to evaluate the association and causation between these two diseases. From the limitation in literature gap, future research is to improve the search engine and evaluate the effectiveness of statistic methods for these data when clinical data resources are limited and difficult to manage. To solve the shortcoming of evidence due to the study design as well as the statistical analysis for new study design, we develop a longitudinal experiment to measure the change of AHI in HNC patients with OSA before, during and after treatment. The next section will propose a longitudinal data analysis that support to analyze the data that we are currently collecting from Sanford hospital.

4. LONGITUDINAL DATA ANALYSIS: METHOD TO EVALUATE THE CHANGE RATE OF AHI IN OBSTRUCTIVE SLEEP APNEA PATIENTS WITH DISCONTINUOUS TREATMENT

4.1. Abstract

Obstructive sleep apnea (OSA) is a common chronic disordered among adults. Due to chronic conditions, the change of OSA severity over time should be managed. Currently, the management of OSA outcomes in adults are includes OSA diagnosis, treatment, and comorbidities. In this study, a framework was proposed to determine the potential clinical features in a high dimension database which affect the AHI and predict the changes of AHI before, during and after a specific treatment. The evaluation of this framework was conduct by the database from Wisconsin Sleep Cohort (WSC) suggested the percentage of AHI different between before-during and during-after taken a depression medication are significantly different.

4.2. Introduction

Obstructive sleep apnea (OSA) is a serious respiratory disorder which indicates by the interruption of breathing during sleep[96]. It is the result of the repetitive collapse of the upper airway that leads to intermittent hypoxia and sleeps fragmentation. Typically, OSA signs and symptoms include the occurrence of excessive daytime sleepiness, loud snoring, abrupt awakenings accompanied by gasping or choking, and difficulty concentrating during the day. OSA, defined by the presence of at least 5 obstructive respiratory events including apneas, hypopneas, or respiratory effort-related arousals. Accordingly, OSA patients without diagnosis or treatment may lead to several outcomes for patients including increased cardiovascular disease, stroke, excessive daytime sleepiness, traffic accidents, and death [97]. In addition, OSA is a chronic illness that requires long-term health care and is also shared across chronic

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conditions, including clinical management, demands of patients, and family. Furthermore, OSA patients often have multiple comorbidities including obesity diabetes, cardiovascular disease, hypertension, and depression. In clinical care, patients with chronic conditions and multiple comorbidities require comprehensive management. Therefore, besides OSA management, OSA patients with comorbidities also need to receive coordinated treatment with disease management processes for other chronic conditions. To increase the efficiency of health care for these chronic disease patients, an evaluation of the influences and relationship between OSA and its comorbidities especially the effect of medication, and treatment on the OSA severity of patients. In this study, we aim to propose a framework that can determine how a treatment changes the AHI and predict the change rate of AHI over time under these treatment conditions.

In particular, the framework was developed to solve the common challenges in analyzing a clinical database. Firstly, clinical, or biomedical databases have more features than observations while a model only requires appropriate variables for inclusion. Thus, we use some common automatic feature selection methods to determine the clinical factor that affects the AHI of OSA patients and find the best group to predict the change in AHI over time. Secondly, patients in long-time research might not receive continuous treatment. In addition, the prediction of treatment effects before-during and after is important for doctors in choosing a suitable treatment as well as taking care of patients undergoing and after therapy. Therefore, the development of this framework also concentrated on evaluating the change rate of AHI in OSA patients in two groups: before-during and during - after the treatment.

4.3. Method

4.3.1. Online Database

In this study, the available online database: Wisconsin Sleep Cohort (WSC) Study was used to demonstrate our algorithm WSC study is a longitudinal, community-based study of the causes, consequences, and natural history of sleep behaviors and common sleep disorders in adults[86]. Since our study aims to evaluate the AHI of the OSA group, 602 individuals were included. Among these individuals, we focus on the group of patients without OSA treatments to control the effect of these treatments on the AHI of patients. In addition, only patients who participated more than one time were considered. All patients received the same sleep overnight protocols, which included PSG, height, weight, BP, body habitus measurements, and questionnaires on lifestyle, health, and medications were conducted at the University of Wisconsin Hospitals and Clinics.Details of the in-laboratory Polysomnography technique are provided in the online supplementary material of WSC database. Apnea categories were examined as the independent variable with AHI < 5: Non-Apnea, AHI >=5: Apnea [87]

4.3.2. General experiment procedure

To develop an efficient methodology, an understanding of experimental design plays an important role to decide the workflow and type of model. The research focuses on the longitudinal data of OSA patients with a discontinuous treatment for a comorbidity of OSA. In this experiment, patients come hospital and receive sleep measurement from 2- 3 times. Each of measurement, besides sleep reports, patients also report several questionnaires relative to demographics, sleep behavior, medical history, life behavior. In addition, patients also take some common laboratory tests and vital sign measurement. Figure 6 describes the workflow of these

experiment; a mathematical model is provided to estimate the major characteristic of this experiment.
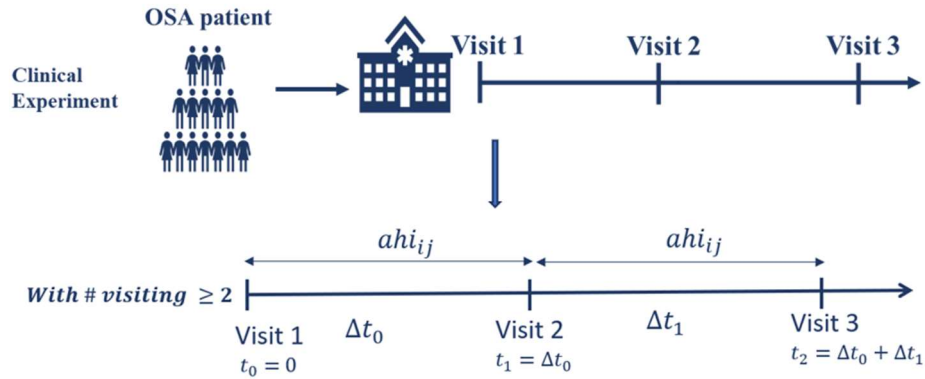

Figure 6: Clinical experimental Design and Mathematical model of the experiment

To explore the information from a longitudinal data, the study proposed a procedure (Figure 6).). In clinical research, the first challenge is the numerous observed variables that typically more than the observation and it is difficult to define what is a good predictor for the interested variable. Hence, first, the variable selection should be provided. Due to the goal of this research is to determine the effect of treatment on AHI progression, so we decide to define a target treatment and predictor that affect the changes of AHI. To eliminate the bias, the treatment was decided by the literature review and randomly choose to depend on the available information of this database. In this case, we choose depression medication is a target treatment need to be evaluated. By the procedure of this medication and the questionnaire information, it was assumed when patients measure their sleep is during depression treatment. In addition, the patients without this treatment will be removed out of our data. In addition, based on the observation of this treatment, there are four different types of treatment status between two sleep measurement in database: $(0 \rightarrow 0), (0 \rightarrow 1), (1 \rightarrow 0), and (1 \rightarrow 1), 0 :$ *no medication*; $1 :$ *using medication.*

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Besides, the other predictors were determined by performing the best subset selection method by using 'leaps' packages. The best set of predictors is quantified by residual sum of square (RSS) error. **Best subset selection** is a method aims to find the subset of independent variables (X_i) that best predict the outcome (Y_i). To perform this method, it will consider all possible combinations of independent variables. Actually, with p predictors, this method will fit all p model for exactly one predictor, all models that contain exactly two predictors, and so on. the algorithm of best subset selection followed Table 7. In this research, we use the 'leaps' package in R to performs an exhaustive search for the best subsets of variables. Due to the limitation of patients, we set the maximum size of subsets to examine in this algorithm is 5 predictors.

Table 7: The general best subset section

Algorithm: Best subset selection [88]
Let M_o denote the null model, which contains no predictor
For $k = 1,2, ..., p; p = 95$ (observed from database)
Fit all $\binom{p}{k}$ models that contain exactly k predictors
Pick the best M_k among these $\binom{p}{k}$ models, M_k is defined with smallest RSS, or largest R^2
Select a single best model from among $M_o, ..., M_k$ using cross validated prediction error, C_p (AIC), BIC, or adjustted R^2

Besides, this step also uses the 'Boruta' packages-a wrapper algorithm around random forest for determining the importance of variables and providing feature selection and in R. The 'Boruta' algorithm consist of 9 steps (Table 8):

Table 8: Summary of Boruta packages algorithm

Algorithm: Boruta packages [89]
Extend the information system by adding copies all variables
Shuffle these variables to remove their correlations with the respone
Run a random forest classifier on the extend information system and gather Z scores.
Estimate the maximum Z score among shadow attributes (MZSA), and then assign a hit to every attribute that scored better than MZSA.
Perform a two-sided test of equality with the MZSA for each attribute undetermined importance.
Remove unimportant predictors that have the importance significantly lower than MZSA
Define the important predictors that have importance the significantly higher than MZSA
Remove shadow attributes
Repeat until the importance is assigned for all the attributes, or the algorithm has reached the previously set limit of the random forest runs.

Since the limit of number of included patients, only 4-5 predictors are considered, therefore, to control the number of accepted features, p-value = 0.0001 was defined. After collecting necessary features, the statistical analysis to conduct evaluate the effect of treatment as well as the interaction of predictors with AHI and target treatment. According to the statistical analysis, several model will develop by the input of predictors to a linear mixed model respectively by its importance. Compare the statistical value of each model and the effect of treatment status and predictors to the rate of change of AHI to find the optimal model and conclude the effect of depression medication and clinical features. The predictors that were observed from the features selection stage are analyzed by correlation testing (continuous variables) and association testing (chi-squares test). Due to the limit of sample size, one of the high correlation variables will be randomly selected instead of all variables. In terms of evaluating the effect of treatment, the rate of change of AHI from four groups of medication status is compared by ANOVA. In addition, the t-test is used to compare whether the mean of these rates is equal to 0. Consequently, the results of these tests decide the model design.

Since this model concentrated on estimating the correlation structure of the rate of changes, Linear Mixed Effects Regression (LMER) model is considered to estimate these key points. This model is an extension of simple linear models that can capture both fixed and random effects. A fixed effect is a parameter that does not vary over time. In contrast, random effects are parameters that are themselves random variables. In general, the theory of linear mixed model following:

$$y = X\beta + Zu + \varepsilon$$

Where y is $N \times 1$ column vector, the outcome variable, X is a $N \times p$ matrix of p predictor variables, β is a $p \times 1$ column vector of fixed -effects regression coefficients; Z is the $N \times qJ$ design matrix for the q random effects and J groups. u is a $qJ \times 1$ vector of a q random effects for J groups; and ε is a $N \times 1$ column vector of residuals. In summary, the prediction model will be adjusted by the properties of database and the predictors (time-varying and time-invariant predictors)
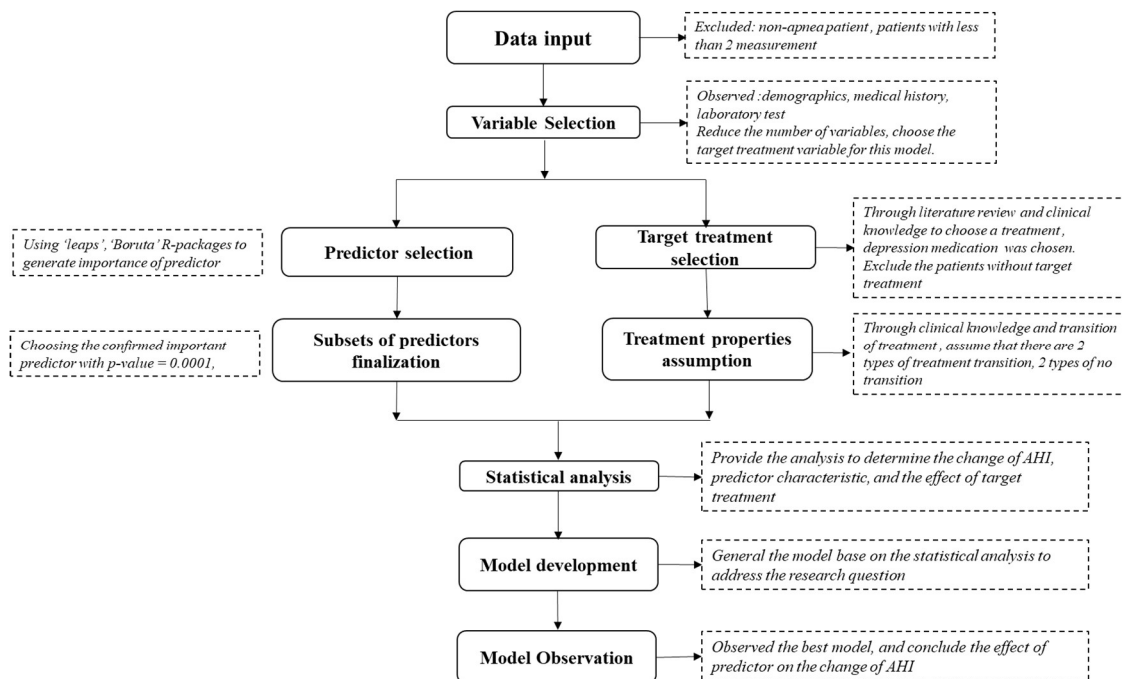

Figure 7: Model development procedure

4.4. Results

By choosing the target treatment (depression medication), 65 individuals were included in the design stage of the model, and each of them had 141 clinical features. The final observation of predictor selection provided 8 significant predictors including: Gender, BMI, State-Trait Anxiety Inventory (State Anxiety Subscale) Score, mean of neck girth measures, Waist to hip ratio, Mean of seated diastolic pressures, Zung Depression. Details of feature selection evaluation will be provided in Appendix. Table 9 performs the descriptive statistic by treatment status and observed predictors. In summary, the focuses groups occur at elder people (age 42-81). All of subjects have overweight or obese (BMI>25), number of females are greater than males in 4 groups. The State -Trait Anxiety is range from 20-49 indicating the moderate to severe anxiety. The systolic pressure is in normal range with elder people from 97 -169, the Zung score is varying from no depression to mild depression. Rate of change of AHI in each group are likely similar, however, the range in group 2 and 3 (having transition in medication status) more fluctuate than the group 1, 4 (no transition in medication status). Table 9 performs the comparison to address whether medication status change the AHI will change by compare the rate of AHI with 0. Table 10 evaluates the difference between provided groups. Accordingly, the rate of AHI in group 2 significantly changes over the time. AHI change rate between group 2,3 is significantly different that illustrates the effect of medication on before-during treatment is different with during-after. In addition, it also suggests that the rate of AHI during-after treatment is significantly different with patients without treatment and always receive treatment. Due to the group 1,4 are not significantly different and AHI rate in these groups are not different to 0 so we assume that the effect of these group is equal to 0. Table 12 performs the results of

longitudinal model. The models suggested that AHI of these patients changes over the time,

Zung score, types of transition and BMI correlated and significantly affect the rate of AHI.

Table 9: Descriptive statistic by treatment status and observed predictors

Characteristic	Depression medication transition			
	Type 1 (0 → 0)	*Type* 2(0 → 1)	*Type* 3 (1 → 0)	*Type* 4 (1 → 1)
Age, mean(range)	60.4(55-70)	60.38(42-81)	58.15(43-71)	61.25(48-74)
BMI: mean (range)	30.44(20.5-41.6)	34(21.6-56)	32.41(19.7-45.9)	35.06(24.2-50)
Gender: Male (Female)	6(9)	16(29)	11(16)	8(16)
State-Trait Anxiety Inventory Score: mean (range)	28.96(20-49)	28.51(20-48.4)	27.14(20-44.2)	28.36(20-47)
Mean of neck girth measures mean(range)	37.84(29-46)	38.37(30-47.5)	38.44(30-50)	39.02(32-47)
Waist to hip ratio mean(range)	0.89(0.7-1.05)	0.91(0.75-1.1)	0.9(0.687-1.11)	0.91(0.77-1.17)
Mean of seated systolic pressures mean(range)	122(97-141)	126.2(94-169)	123.7(94-153)	127.5(108-146)
Zung Depression mean(range)	32.27(23-53)	33.8(20-59)	33.11(22-55)	32(24-48)
Rate of AHI change in each transition, mean(range)	1.31(-0.92-10.14)	2.2(-1.94-43.88)	1.3(-0.88-20.33)	0.91(-0.9-13.26)

Table 10: Evaluating the effect of medication on the change of AHI

t-test (compare rate of change of AHI)	Depression medication transition			
	Type 1 (0 → 0)	*Type* 2(0 → 1)	*Type* 3 (1 → 0)	*Type* 4 (1 → 1)
Compare mean with 0, p-value	0.08578	0.03338 *	0.1197	0.1219

(*: p-value <0.05)

Table 11: Testing the difference between group of treatment transition

Compare AHI change rate between group	p-value
Group 1 and Group 4	0.5811
Group 2 and Group 3	0.008344*
Group 2 and (Group 1+ Group 4)	0.3178
Group 3 and (Group 1+ Group 4)	0.01429*
All groups	0.508

(*: p-value <0.05)

Table 12: The results of model

Model	Estimate	P-value
Intercept	6.001364	0.2194
Δt	-1.314452	0.1154
type 1	-20.909293	0.0003*
type 2	-0.321642	0.9585
zung_score	0.077124	0.4944
genderM	-1.138413	0.1984
state	0.062261	0.3755
bmi	-0.100846	0.1094
Δt x type 1	2.633593	0.0060 *
Δt x type 2	1.794070	0.0999
type1 x zung_score	0.301794	0.0275*
type2 x zung_score	-0.211195	0.1652

(*: p-value <0.05)

4.5. Discussion

The traditional longitudinal model to evaluate the relationship between OSA and other clinical factors typically follow a standard experiment with equal time spaces. In this case, the model often develops as multivariable linear model to evaluate the effect of predictor on AHI value. However, in fact, the patients will check-in hospital randomly, therefore, one of the challenges in this research is the time duration between each measurement is flexible. In addition, with the longitudinal research with more than 1-year changes between each measurement, the medical history as well as the demographic will change over time. Hence, to provide a good model to support the OSA and its comorbidities management, both mentioned problems need to be considered.

In addition, estimating the change rate of AHI will suggest a potential prediction for physicians and doctors when deciding on treatment for patients as well as managing the progression of these disorders. Accordingly, our model measures the change of AHI for the following visit of patients, so from the results of patients in the first came, it is possible to predict what will happen with patients if they receive a medication or a treatment. This observation provides more evidence for doctors and patients to decide what type of treatment is good for their health. In this study, our model assumes that the clinical predictors are independent. It might not describe exactly the relationship as well as the interaction between these variables. In future research, this limitation can be solved by investigating more about these interactions.

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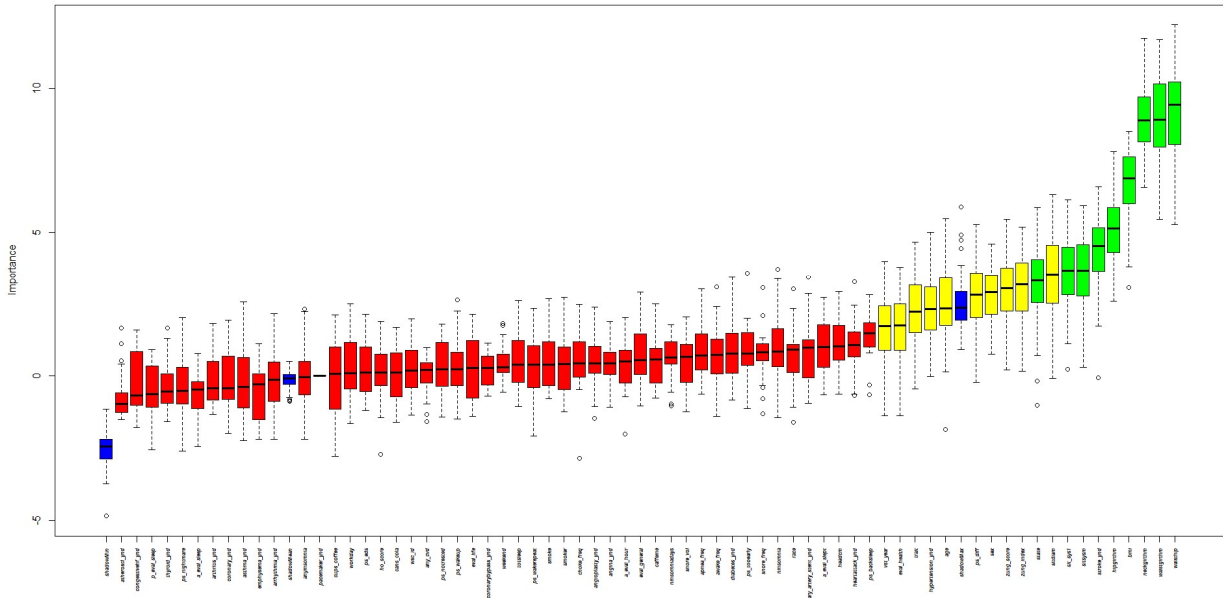
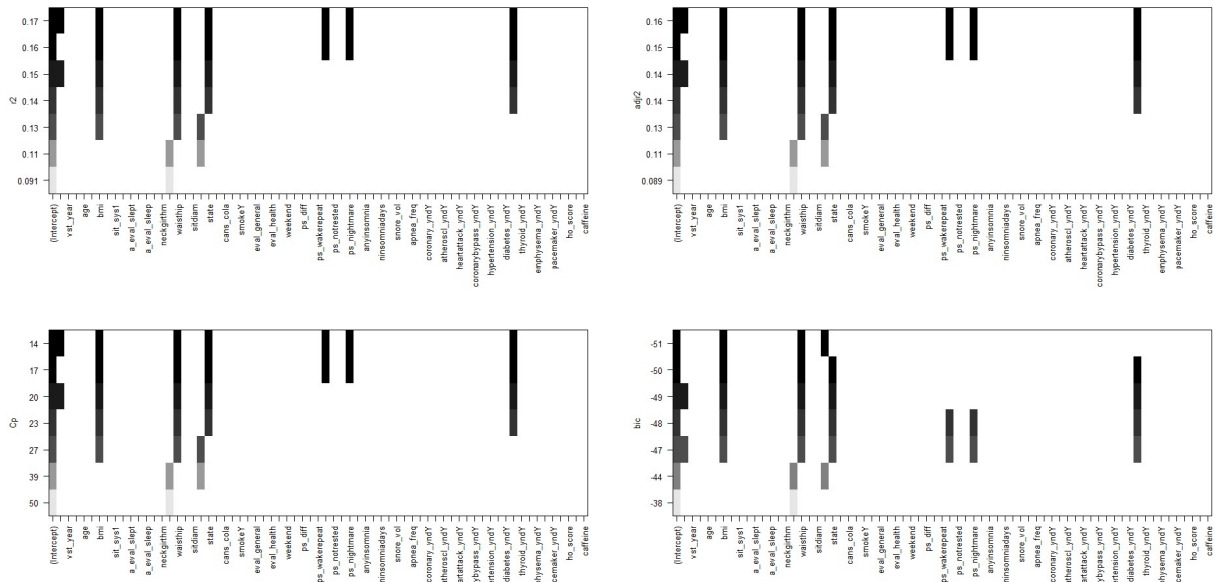Figure A1: Importance of variables

Figure A2: The selected variables for the best model with a given number of predictors, ranked according to the R^2 , adjusted R^2, Cp, BIC