# Overview of Obstructive Sleep Apnea and Neutrophil-Lymphocyte Ratio

**Madiha Mohamed Kotkat[1], Yahia Ali Aboshab[1], Samir Sorour Sorour[1], Amal Ahmed Zidan[2], Said Abdelmoniem Mohamed[1], Ahmed Fouad Elgohary[1]**

**[1]Otorhinolaryngology Department, Faculty of Medicine, Zagazig University, Egypt.**
**[2]Clinical Pathology Department, Faculty of Medicine, Zagazig University, Egypt.**
**Corresponding author: Madiha M. Kotkat**,Email:Madehakotkat1@gmail.com

**ABSTRACT**

Obstructive sleep apnea (OSA) is a serious health problem associated with cardiovascular diseases, neurological diseases, and various types of mortality. Obstructive sleep hypopnea occurs when breathing is diminished, even if it is not absent. Sleep destabilizes patency of the upper airway leading to partial or complete obstruction of the nasopharynx, oropharynx, or both.Diagnosis is based on sleep history and polysomnography. Many options of treatment including nasal continuous positive airway pressure, oral appliances, and, in refractory cases, surgery and theprognosis is good with treatment. However, most cases remain undiagnosed and untreated and are often associated with hypertension, atrial fibrillation and other arrhythmias, heart failure, and injury or death due to motor vehicle crashes and other accidents resulting from hypersomnolence. Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) is calculated from complete blood count with differential, WBCs, widely available marker of inflammation that might assist in identifying patients with obstructive sleep apnea. Thus, the aim of the current study was to review the relation between NLR and outcome of OSA surgery in adults.

**Keywords:** Neutrophil-Lymphocyte Ratio; Obstructive Sleep Apnea;Diagnosis
**DOINumber:10.48047/nq.2022.20.19.NQ99335** **NeuroQuantology2022;20(19):3734-3746**



## Introduction

Obstructive sleep apnea (OSA) consists of episodes of partial or complete closure of the upper airway that occur during sleep and lead to breathing cessation (defined as a period of apnea or hypopnea > 10 seconds). Symptoms include excessive daytime sleepiness, restlessness, snoring, recurrent awakening, and morning headache**(1)**.

The prevalence of obstructive sleep apnea is 2 to 9% in adults; the condition is under-recognized and often undiagnosed even in symptomatic patients. Obstructive sleep apnea is up to 4 times more common among men and 7 times more common among people who are obese (ie, body mass index [BMI] > 30). Severe OSA (apnea-hypopnea index [AHI] > 30/hour) increases the risk of death in middle-aged men **(2)**.

Obstructive sleep apnea is the leading medical cause of excessive daytime sleepiness (sometimes called wake-time sleepiness), increasing risks of automobile crashes, loss of employment, and sexual dysfunction. Relationships with bed partners and roommates and/or housemates may

also be adversely affected because affected people may also have difficulty sleeping **(3)**.

Long-term cardiovascular sequelae of untreated OSA include poorly controlled hypertension, heart failure, and atrial fibrillation (even after catheter ablation) and other arrhythmias**.** OSA also increases the risk for nonalcoholic fatty liver disease, likely due to intermittent nocturnal hypoxia and sleep disruption **(2,4).**

**Etiology & Epidemiology of OSA:**

The aetiology of OSA is multifactorial, which comprises of complex interactions between anatomical and neuromuscularfactors leading to upper airway collapsibility**(1)**.Inspiratory efforts against a closed upper airway cause paroxysms of inspiration, reductions in gas exchange, disruption of normal sleep architecture, and partial or complete arousals from sleep. These factors interact to produce morbidity and mortality through hypoxia, hypercapnia, and sleep fragmentation **(2)**.

OSA is an extreme form of sleep-related upper airway resistance. Less severe forms that do not cause oxygen desaturation include snoring, upper airway airflow resistance causing noisy inspiration but without sleep arousals and upper airway resistance syndrome, characterized by crescendo snoring terminated by respiratory effort-related arousals (RERAs)**(1)**.

OSA is most common among older males, but it can also affect women and children. The incidence rises following menopause such that rates are similar in postmenopausal women and men **(5).**

The estimated prevalence in North America is approximately 15 to 30 percent in males and 10 to 15 percent in females, when OSA is defined broadly as an apnea-hypopnea index (AHI) greater than five events per hour of sleep **(6).** When more stringent definitions are used (eg, AHI ≥5 events per hour plus symptoms or AHI ≥15 events per hour), the estimated prevalence is approximately 15 percent in males and 5 percent in females. Global estimates using five or more events per hour suggest rates of 936 million people worldwide with mild to severe OSA, and 425 million people worldwide with moderate to severe OSA, between the ages of 30 and 69 years of age **(7).**

The prevalence of OSA also varies by race. OSA is more prevalent in African Americans who are younger than 35 years old compared with Caucasians of the same age group, independent of body weight. The prevalence of OSA in Asia is similar to that in the United States, despite lower rates of obesity **(8).**

The prevalence appears to be increasing and may relate to the increasing rates of obesity or increased detection rates of OSA. In one study, the estimated prevalence of OSA between 1990 and 2010 increased from 11 to 14 percent in adult males and from 4 to 5 percent in adult females. Another study from the United Kingdom also demonstrates a significant increase in the rates of OSA and obesity between 1994 and 2015 **(9).**



**Risk factors and associated conditions of Obstructive Sleep Apnea:**

Several clinical risk factors are associated with OSA and include the following: **(9)**

- **Age:** the prevalence of OSA increases from young adulthood through the sixth to seventh decade, then appears to plateau.
- **Ggender :**OSA is approximately two to three times more common in males than females, although the risk appears to be similar once women are peri- and post-menopausal.
- **Obesity :**The risk of OSA correlates well with the body mass index (BMI). In one study, a 10 percent increase in weight was associated with a six-fold increase in risk of OSA. In another study, moderate to severe OSA (apnea-hypopnea index [AHI] ≥15) was present in 11 percent of men who were normal weight, 21 percent who were overweight (BMI 25 to 30 kg/m2), and 63 percent of those

who were obese (BMI >30 kg/m2). Similarly, in women, OSA was present in 3 percent of patients who were normal weight, 9 percent of those who were overweight, and 22 percent of those who were obese. The majority of individuals with obesity hypoventilation syndrome (OHS) have OSA (90 percent); OHS is discussed separately **(9).**

- **Craniofacial and upper airway abnormalities:** increase the likelihood of having OSA. These factors are best recognized in Asian patients where obesity is not as major a risk factor compared with the United States. Examples of abnormalities include an abnormal maxillary or short mandibular size, a wide craniofacial base, and tonsillar and adenoid hypertrophy, the latter being common in children **(10)**.
- **Smoking** may increase the risk of or worsen OSA. In one study, current smokers were nearly three times more likely to have OSA than past or never smokers**(9)**.
- **Family history of snoring or OSA** due to shared behavioral or environmental factors, there may also be a genetic predisposition to OSA through factors such as craniofacial structure. It has been suggested that about 40 percent of the variance of the AHI has a genetic basis. In another study of rural Brazilians, the heritability of an AHI >5/hour was intermediate (25 percent) **(10)**.
- **Others**: Nasal congestion confers an approximately two-fold increase in the prevalence of OSA compared with controls, regardless of the cause. However, OSA may or may not improve with correction of nasal congestion. Exposure to high levels of environmental nitrogen dioxide and particulate matter may contribute to variations in OSA among patient populations **(11)**.While a variety of substances and medications, including alcohol, benzodiazepines, narcotics, and possibly gabapentinoids may exacerbate OSA, a causative link is unproven **(12)**.

The prevalence of OSA is also increased in patients with a variety of medical conditions, including the OHS, congestive heart failure, atrial fibrillation pulmonary hypertension, hypertension (particularly resistant hypertension), cardiovascular disease, atrial fibrillation, and pulmonary hypertension, end-stage kidney disease, hronic lung disease, including asthma, chronic obstructive pulmonary disease (COPD), and idiopathic pulmonary fibrosis, stroke and transient ischemic attacks, pregnancy, gestational diabetes pregnancy-induced hypertension acromegaly, hypothyroidism, polycystic ovary syndrome and parkinson's disease**(13-17)**.

**Pathophysiology of OSA:**



Similar to the clinical heterogeneity, OSA pathogenesis is also multifactorial. There are "anatomical" and "non-anatomical" causes. In recent years, the potential role that factors beyond pharyngeal anatomy and craniofacial structure play in OSA pathophysiology has been recognized. Indeed, OSA can develop due to multiple contributors, the combination of which likely varies substantially between patients**(2)**. Non-anatomical contributors include impaired pharyngeal dilator muscle function, premature awakening to mild airway narrowing (low respiratory arousal threshold), and unstable control of breathing (high loop gain)**(Figure 1)(14)**.

As highlighted in later sections, when combined with a pharyngeal airway that is susceptible to closure during sleep, impairment in one or more of these non-anatomical contributors can perpetuate OSA severity. Given that airway obstruction in OSA only occurs during sleep, the combination of an anatomical predisposition combined with state-dependent changes in non-anatomical

contributors is crucial in driving this common disorder**(15)**.

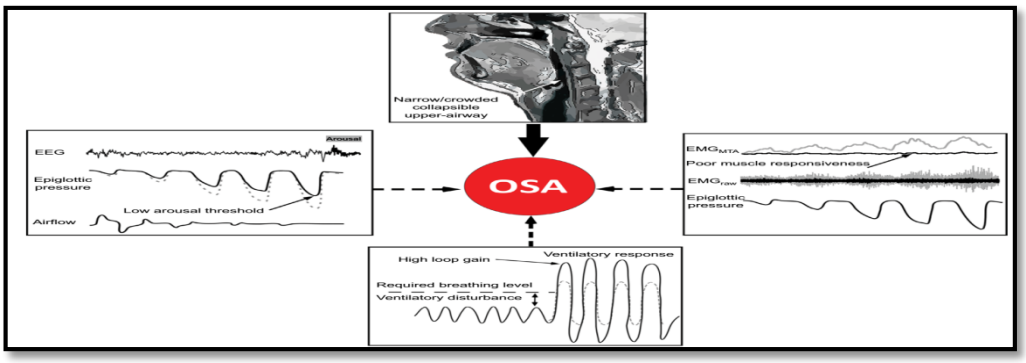


**Figure (1): Schematic of the anatomical and non-anatomical causes of OSA.**

**Clinical Features of OSA:**

Most patients with OSA complain of daytime sleepiness, or their bed partner reports loud snoring, gasping, choking, snorting, or interruptions in breathing while sleeping. These symptoms are often detected during the evaluation of another complaint, or during health maintenance or preoperative screening**(10)**.

Daytime sleepinessis a common feature of OSA. Sleepiness is the inability to remain fully awake or alert during the wakefulness portion of the sleep-wake cycle. Daytime sleepiness may be underestimated because of its insidious onset and chronicity. The patient may use terms such as fatigue, tiredness, low energy, or poor focus. Targeted questioning of the patient and in particular their loved ones or bed partner, however, typically reveals a pattern of feeling sleepy or falling asleep in boring, passive, or monotonous situations. As an example, the patient may admit to consistently falling asleep while reading, watching television, or even while operating a motor vehicle. In addition, embarrassing or inappropriate episodes of sleep may be reported (eg, at religious services, listening to lectures, or driving). Reviewing patient behavior away from the workplace is essential because daytime sleepiness can be masked by activity. Patients should also always be asked about behaviors that may mask sleepiness, such as caffeine consumption. Patients often experience nonrestorative sleep (ie, do not wake up feeling refreshed) and nocturnal restlessness in association with their complaint of daytime sleepiness **(18)**.

Sleepiness should be distinguished from fatigue. Fatigue is defined as a subjective lack of physical or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities. To facilitate this distinction, a series of directed questions can be combined with the Epworth Sleepiness Scale (ESS) to quantitatively document the patient's perception of sleepiness, fatigue, or both. An ESS score >9 indicates abnormal sleepiness and should prompt further testing. Since there is often overlap of both sleepiness and fatigue in patients with OSA, our center administers both the ESS and the Fatigue Severity Scale (FSS) to help identify and manage these complaints **(19)**.

**Diagnostic Evaluation:**

OSA should be suspected whenever a patient presents with excessive daytime sleepiness, snoring, and choking or gasping during sleep, particularly in the presence of risk factors such as obesity, male gender, and advanced age. Less common manifestations are early morning headaches, or manifestations of associated disorders (eg, hypertension) or complications (eg, neuropsychiatric symptoms)**(12)**.

Detailed questions that explore the etiologies of daytime sleepiness, snoring,

and neuropsychiatric disease may help to tease out OSA from other conditions but sleep apnea testing is required to make the diagnosis of OSA. Details regarding taking a targeted history and performing a comprehensive examination in patients with daytime sleepiness is provided separately**(16)**.

There has been debate in the literature regarding whether non-sleep experts can adequately evaluate patients with suspected OSA **(20)**. While observational studies have suggested that evaluation by sleep and non-sleep experts may be similar, many of the non-sleep specialists in these studies have extensive training or experience in sleep medicine. Accordingly, in support of the American Academy of Sleep Medicine (AASM) guidelines, a comprehensive evaluation with follow-up by a clinician who has some level of expertise in sleep medicine is appropriate **(21)**.

OSA is not a clinical diagnosis and objective testing must be performed for the diagnosis. Due to the wide differential associated with the symptoms of OSA, several clinical criteria and data from evaluation tools are used to select those who should be tested**(22)**.

Diagnostic testing for OSA should be performed on patients with excessive daytime sleepiness (EDS) on most days and the presence of at least two of the following clinical features of OSA: habitual loud snoring, witnessed apnea or gasping or choking during sleep, and diagnosed systemic hypertension **(21)**.

**Diagnosis of Obstructive Sleep Apnea**

The diagnosis of OSA is based upon the presence or absence of related symptoms, as well as the frequency of respiratory events during sleep (ie, apneas, hypopneas, and respiratory effort-related arousals [RERAs])**(14)**.

The diagnostic criteria and indices used on official sleep study reports vary according to whether the data are polysomnography (PSG)- or home sleep apnea testing (HSAT)-derived:

1- **PSG**:The diagnosis of OSA is confirmed if either of the two criteria below is present **(23)**:

There are five or more predominantly obstructive respiratory events (obstructive and mixed apneas, hypopneas, or RERAs) per hour of sleep in a patient with one or more of the following Sleepiness, nonrestorative sleep, fatigue, or insomnia symptoms; waking up with breath holding, gasping, or choking, habitual snoring, breathing interruptions, or both noted by a bed partner or other observer, hypertension, mood disorder, cognitive dysfunction, coronary artery disease, stroke, congestive heart failure, atrial fibrillation, or type 2 diabetes mellitus. There are 15 or more predominantly obstructive respiratory events (apneas, hypopneas, or RERAs) per hour of sleep regardless of the presence of associated symptoms or comorbidities.PSG data can generate two indices as quantitative measures of sleep-related obstructive events per hour of sleep:The apnea-hypopnea index (AHI = [apneas + hypopneas] / total sleep time in hours). The respiratory disturbance index (RDI = [apneas + hypopneas + RERAs)] / total sleep time in hours. Because of the inclusion of RERAs, the RDI classifies more patients as having OSA than does the AHI, using the same threshold values.

**2-HSAT**

Most HSAT devices do not include electroencephalogram (EEG) monitoring, and therefore RERAs and hypopneas characterized by arousals cannot be reliably identified. Accordingly, the number of respiratory events per hour of recording time rather than total sleep time is used to generate the respiratory event index (REI). In validated HSAT devices, the REI correlates well with AHI and RDI, but is typically lower since the denominator (ie, total recording time) is larger than total sleep time used to calculate AHI and RDI. Moreover, outcomes in properly selected high risk patients tested

by HSAT are similar to patients undergoing in-laboratory studies. Evidence does show that the length of the recording time used to generate the REI with HSAT should be at least four hours. With these caveats in mind, cutoff values that are used for REI to diagnose OSA are similar to those in whom in laboratory sleep testing is performed. Thus, patients with a REI ≥15 events per hour and REI 5 to 14 and symptoms is supportive of a diagnosis of sleep apnea. Patients with a negative study, inconclusive results or a technically inadequate study should be evaluated in a laboratory setting. Differences among portable devices are discussed separately**(24)**.

**Classification of severity**

Patients who meet criteria for a diagnosis of OSA are traditionally classified as having mild, moderate, or severe disease on the basis of the AHI and symptoms. This classification is based on consensus, and depending on definitions of "hypopnea," there can be great variance in the AHI. With increasing use of HSAT, similar stratification is being used for REI. This is, however, also arbitrary. Moreover, the literature is confusing, often interchanging AHI for RDI**(25)**.

Patients traditionally classified as having mild OSA are those with an AHI/RDI/REI between 5 and 14 respiratory events per hour of sleep. Such patients may be relatively asymptomatic or report sedentary (ie, passive) daytime sleepiness, becoming noticeable once the patient is unstimulated. The daytime sleepiness often does not impair daily life, although it may be recognized by family members. Alternatively, daytime sleepiness may become apparent to the patient only after it improves due to weight loss, alcohol abstinence, or treatment of OSA. The sleep stages and slow wave sleep are generally preserved in mild OSA. Even when asymptomatic, mild OSA is associated with increased risk of hypertension, and this becomes a stronger association at younger ages **(26)**. However, using the latest AASM definition of hypopnea, symptomatic patients with mild OSA are without increased cardiovascular risk **(27)**.

Patients classified as having severe OSA are those with an AHI/RDI/REI greater than 30 respiratory events per hour of sleep. Such patients more often have daytime sleepiness that interferes with normal daily activities. They tend to fall asleep often during the day (in a sitting posture) and are at risk for accidental injury from sleepiness. Patients with severe OSA are at increased risk for all-cause mortality and a variety of cardiovascular comorbidities, including hypertension, coronary artery disease, and arrhythmias**(25)**.



**Upper airway resistance syndrome**

Upper airway resistance syndrome (UARS) occurs when airflow limitation due to increased upper airway resistance (ie, RERAs) induces arousals from sleep, leading to excessive daytime sleepiness. More commonly, the presence of prolonged partial upper airway obstruction is a common phenotype of sleep-disordered breathing, and is underreported **(28)**.

In one study of patients referred for polysomnography, 29.9 percent presented with OSA, whereas 10.8 percent had prolonged partial obstruction with a normal AHI **(29)**. During recordings of nasal airflow, periods of flow limitation longer than a hypopnea (minimum one to three minutes) are often used as indicative of sustained upper airway resistance **(28)**. However, there is no consensus about the optimal detection, proper measurement, or degree of clinical impact. A PSG rather than HSAT is recommended for the detection of UARS, since it is better at identifying prolonged flow limitation via the nasal cannula.

Thus, the study may be interpreted as absent or mild OSA, requiring no treatment. Partial upper airway obstruction is treatable with nasal continuous positive airway pressure (CPAP) and patients have good adherence to therapy **(28)**.

**Prognosis for Obstructive Sleep Apnea**

Prognosis of obstructive sleep apnea is excellent if effective treatment is instituted**(3)**.Untreated or unrecognized obstructive sleep apnea can lead to cognitive impairment as a result of sleeplessness, which, in turn, can lead to serious injury or death caused by accidents, especially motor vehicle crashes. Sleepy patients should be warned of the risks of driving, operating heavy machinery, or engaging in other activities during which unintentional sleep episodes would be hazardous**(1)**.

Adverse effects of hypersomnolence, such as loss of employment and sexual dysfunction, can affect families considerably**(13)**.In addition, perioperative complications, including cardiac arrest, have been attributed to OSA, probably because anesthesia can cause airway obstruction after a mechanical airway is removed. Patients should therefore inform their anesthesiologist of the diagnosis before undergoing any surgery and should expect to receive continuous positive airway pressure (CPAP) when they receive preoperative drugs and during recovery **(30)**.

**Treatment of Obstructive Sleep Apnea**

Control of risk factors such as obesity, hypertension, alcohol use, and sedative use.Continuous positive airway pressure (CPAP) or oral appliances. For anatomic encroachment or disease that does not respond to devices, surgery, or nerve stimulation. The aim of treatment is to reduce episodes of hypoxia and sleep fragmentation; treatment is tailored to the patient and to the degree of impairment. Success is defined as a resolution of symptoms with AHI reduction below a threshold, usually 10/hour.Treatment is directed at both risk factors and at obstructive sleep apnea itself. Specific treatments for obstructive sleep apnea include continuous positive airway pressure (CPAP), oral appliances, and airway surgery**(15,16,20)**.

**I. Control of risk factors**

Initial treatment aims at optimal control of modifiable risk factors for obstructive sleep apnea, including obesity, hypertension, alcohol and sedative use, hypothyroidism, acromegaly, and other chronic disorders. Although modest weight loss (15%) may result in clinically meaningful improvement, weight loss is extremely difficult for most people, especially those who are fatigued or sleepy. Bariatric surgery frequently reverses symptoms and improves AHI in morbidly obese (BMI > 40) patients; however, the degree of these improvements may not be as great as the degree of weight loss. Weight loss, with or without bariatric surgery, should not be considered a cure for OSA (**30)**.

**II.Continuous positive airway pressure (CPAP)**

Nasal continuous positive airway pressure is the treatment of choice for most patients with OSA and subjective daytime sleepiness; adherence is lower in patients who do not experience sleepiness. CPAP improves upper airway patency by applying positive pressure to the collapsible upper airway segment. Effective pressures typically range from 3 to 15 cm water. Disease severity does not correlate with pressure requirements. Many CPAP devices monitor CPAP efficacy and titrate pressures automatically, according to internal algorithms. If clinical improvement is not apparent, CPAP efficacy should be reviewed and patients should be reassessed for a second sleep disorder (eg, upper airway obstruction) or a comorbid disorder. If necessary, pressure can be titrated manually during monitoring with repeat polysomnography. Regardless of improvement in the AHI, CPAP will reduce cognitive impairment and improve quality of life, and it may reduce blood pressure. If

CPAP is withdrawn, symptoms recur over several days, though short interruptions of therapy for acute medical conditions are usually well tolerated. Duration of therapy is indefinite **(8,31)**.

Failures of nasal CPAP are common. Attention should be given to improving adherence by overcoming inherent bias, early attention to problems and mask fit, and close follow-up by a committed caretaker. If patients have septal deviation, septoplasty may make treatment more successful. There is also a need to recognize and address the decreased long-term CPAP adherence among patients who are not obese but have low respiratory arousal sleep threshold and the related propensity for increased arousals and irregular breathing **(3)**.

**III.Oral appliances**

Oral appliances are designed to advance the mandible or, at the very least, prevent retrusion during sleep. Some appliances are also designed to pull the tongue forward. Use of these appliances to treat both snoring and mild to moderate obstructive sleep apnea is gaining acceptance. Comparisons of appliances to CPAP show equivalence in mild to moderate obstructive sleep apnea, but results of cost-effectiveness studies are not available**(7)**.

**IV.Surgery:**

Surgical procedures to correct anatomic factors such as enlarged tonsils and nasal polyps contributing to upper airway obstruction (called anatomic procedures) should be considered. Surgery for macroglossia or micrognathia is also an option. Surgery is a first-line treatment if anatomic encroachment is identified. However, in the absence of encroachment, evidence to support surgery as a first-line treatment is lacking**(13)**.

Uvulopalatopharyngoplasty (UPPP) was the most commonly used procedure. It involves resection of pharyngeal tissue. UPPP has been largely replaced by less aggressive approaches that might stabilize the lateral walls of the pharynx and/or enlarge the velopharyngeal area without altering speech or swallowing. Equivalence with CPAP was shown in one study using CPAP as a bridge to surgery, but the interventions have not been directly compared. UPPP may not be successful in patients who are morbidly obese or who have anatomic narrowing of the airway. Moreover, after UPPP, recognition of sleep apnea is more difficult because of a lack of snoring. Such silent obstructions may cause apneic episodes as severe as those occurring before surgical intervention**(14,15)**.

Other surgical procedures include midline glossectomy, hyoid advancement, and mandibulomaxillaryadvancement that offered as a 2nd-stage procedure if UPPP is not curative. The optimal multistage approach is not known**(30)**.

Tracheostomy is the most effective therapeutic maneuver for OSA but is done as a last resort. It bypasses the site of obstruction and is indicated for patients most severely affected (eg, those with corpulmonale)**(1)**.

Hypoglossal nerve stimulationusing a nonanatomic procedure is upper airway stimulation. In upper airway stimulation, an implanted device is used to activate a branch of the hypoglossal nerve. This therapy can be successful in highly selected patients with moderate to severe disease who are unable to tolerate CPAP therapy and those in whom mandibulomaxillary advancement is contemplated. Experience with this line of therapy is growing, but using appropriate selection criteria is crucial for success**(32)**.

**Adjunctive treatments**

Adjunctive treatments are commonly used but have no proven role as first-line treatment for obstructive sleep apnea. Modafinil can be used for residual sleepiness in OSA in patients who are effectively using CPAP.Supplemental oxygen improves blood oxygenation, but a beneficial clinical effect cannot be

predicted. Also, oxygen may provoke respiratory acidosis and morning headache in some patients**(33)**.

A number of drugs have been tried (eg, tricyclic antidepressants, theophylline, dronabinol, combined atomoxetine plus oxybutynin) but cannot be routinely advocated because of limited efficacy, a low therapeutic index, or absence of replication of results **(33)**. Better methods to recognize sleep apnea subtypes will permit interpretation of successes and failures with this line of treatment**(1,15)**.

Nasal dilatory devices and throat sprays sold OTC for snoring have not been studied sufficiently to prove benefits for OSA**(30)**.

Laser-assisted uvuloplasty, uvular splints, and radiofrequency tissue ablation have been promoted as treatments for loud snoring in patients without obstructive sleep apnea. Although they may transiently decrease snoring loudness, efficacy declines over months to years **(33)**.

An informed patient and family are better able to cope with a treatment strategy, including tracheostomy. Patient support groups provide helpful information and effectively support timely treatment and follow-up**(2)**.

**Neutrophil-Lymphocyte Ratio and OSA Patients**

The scientific community considers biomarkers as a highly promising aspect of medicine. Nowadays, biomarkers are being utilized in the diagnosis of various diseases and in their prognosis as well. They are expected to help in identifying individuals at risk early; and therefore, enabling primary prevention of many of these disorders. The role of the new biomarkers is expected to grow tremendously in the upcoming years. The inexpensive and readily available markers; such as NLR, have a greater potential in diagnosing various diseases **(34)**.Cells of the immune systems play a critical role in the host response to infection. Moreover, their ability to respond dynamically to any acute insult and the feasibility of their sampling raises the possibility that leukocytes might serve as a measure of systemic inflammation **(35)**.

The early hyperdynamic phase of infection is characterised by a proinflammatory state and mediated by neutrophils, macrophages and monocytes, with the release of inflammatory cytokines. The onset of acute neutrophilia is associated with the generation of endotoxin, tumour necrosis factor (TNF), interleukin (IL)-1, IL-8 and haematopoietic growth factors such as granulocyte colony-stimulating factor (GCSF). The maximal response usually occurs within 4–24 hours of exposure to these agents and probably results from the release of neutrophils from the marrow into circulation. The systemic inflammatory response is also associated with suppression of neutrophil apoptosis, which augments neutrophil-mediated killing as part of the innate response, but may also cause tissue injury. Meanwhile, lymphocyte apoptosis increases in the thymus and spleen **(36)**.

Studies of human participants injected with intravenous endotoxin revealed differential expression of more than 2000 transcripts in the neutrophils. There was an upregulation of particular genes involved in inflammation and inhibition of apoptosis. The response was similar to that seen following multiple trauma. In paediatric patients with sepsis, genes related to mitochondrial dysfunction and to redox pathway-related signalling within the neutrophils are maximally upregulated. In contrast, genes involved in an inflammatory response within peripheral blood mononuclear cells (including both monocytes and lymphocytes) were down-regulated, whereas genes involved in apoptosis were upregulated**(35)**.

NLR has been used as a measure of systemic inflammation **(37)**. NLR can be easily calculated and is immediately available from the CBC routinely ordered in admitted patients. Its use in the emergency

settings helps the physician to early identify patients at risk of bloodstream infections and to administer antimicrobials as soon as possible **(38)**. NLR has been proven to be useful in diagnosing bacterial infection among patients hospitalized for fever, bacterial community-acquired pneumonia. It was also found to indicate mortalities in critically-ill patients and to guide the prognosis of various acute infectious conditions, ischemic heart disease, metabolic diseases, cancer and other medical conditions **(39)**.

Meanwhile, in children, NLR was able to distinguish viral from bacterial pneumonia, and also helped in diagnosing acute appendicitis. Moreover, in children with an established diagnosis of familial Mediterranean fever, NLR was found to predict the attacks **(40)**.

Two studies investigated the role of NLR in pediatric UTI **(41,42)**. Han et al performed a retrospective study on 298 pediatric patients (age≤36 months) with febrile UTI, in whom, conventional infection markers (WBC count, ESR, CRP, and NLR) were measured. The study revealed a significant correlation between elevated NLR and DMSA defect of acute pyelonephritis. Furthermore, NLR was suggested as a reliable marker for the prediction of VUR **(41)**.Cortical defects on initial DMSA scan were noted in 133 patients. Vesicoureteral reflux (VUR), white blood cell count, and absolute neutrophil count, NLR, and CRP level were independent predictive factors for a positive cortical defect on initial DMSA scan. On follow-up DMSA scan, 24 of the 133 patients showed persistent cortical defects, and only VUR was significantly associated with a persistent cortical defect. In 84 patients who showed cortical defect on initial scan and absence of VUR, only NLR was significantly associated with a persistent cortical defect on the follow-up scan (**42)**. Importantly, none of the previous studies investigated its role in diagnosing UTI itself.

NLR is readily available, inexpensive and easily calculated marker. The predictive superiority of NLR may be due to many reasons. First, it is less likely to be affected by various physiological conditions such as dehydration and exercise. More importantly, NLR is a ratio of two different yet complementary immune pathways, thus integrating the effects of neutrophilia; which are responsible for active non-specific inflammation and lymphopenia; which is a marker of poor general health and physiological stress. Therefore, since NLR is an integrated reflection of two important immune pathways, it is more predictive than either parameter alone **(34,37)**.

**CONCLUSION:**

Obstructive sleep apnea is becoming more common, which is detrimental to people's quality of life. Although sleep medicine is a relatively new specialty, there has been much advancement in recent years. Future studies should look at the causes of people who have obstructive sleep apnea, as this would help doctors treat their patients more effectively.

Neutrophil-lymphocyte ratio is a quick, cheap, easily measurable inflammatory marker with routine complete blood count analysis, is a marker of obstructive sleep apnea severity. Thus, NLR levels would improve as chronic inflammation diminishes in OSApatients after surgery.

**No Conflict of interest.**

**References:**

1. Paliogiannis P, Deligia, G., Farina, G., Bassu, S., Mangoni, A. A., Zinellu, A. Associations between the neutrophil-to-lymphocyte and the platelet-to-lymphocyte ratios and the presence and severity of psoriasis: a systematic review and meta-analysis. Clin. Exp. Med. 2019;19:37–45.
2. Zinchuk AV, Jeon S, Koo BB. Polysomnographic phenotypes and their cardiovascular implications in obstructive sleep apnoea. Thorax 73(5):472–480, 2018.

**3.** Zinchuk A, Edwards BA, Jeon S. Prevalence, associated clinical features, and impact on continuous positive airway pressure use of a low respiratory arousal threshold among male United States veterans with obstructive sleep apnea. J Clin Sleep Med 14(5):809–817, 2018.
**4.** Musso G, Cassader M, Olivetti C, et al: Association of obstructive sleep apnoea with the presence and severity of non-alcoholic fatty liver disease. A systematic review and meta-analysis. Obes Rev 14:417–431, 2013.
**5.** Young T, Palta M, Dempsey J, et al. Burden of sleep apnea: rationale, design, and major findings of the Wisconsin Sleep Cohort study. WMJ 2009; 108:246.
**6.** Peppard PE, Young T, Barnet JH, et al. Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol 2013; 177:1006.
**7.** Benjafield AV, Ayas NT, Eastwood PR. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. Lancet Respir Med 2019; 7:687.
**8.** Sunwoo JS, Hwangbo Y, Kim WJ. Prevalence, sleep characteristics, and comorbidities in a population at high risk for obstructive sleep apnea: A nationwide questionnaire study in South Korea. PLoS One 2018; 13:e0193549.
**9.** Lechner M, Breeze CE, Ohayon MM, Kotecha B. Snoring and breathing pauses during sleep: interview survey of a United Kingdom population sample reveals a significant increase in the rates of sleep apnoea and obesity over the last 20 years - data from the UK sleep survey. Sleep Med 2019; 54:250.
**10.** Chi L, Comyn FL, Keenan BT, et al. Heritability of craniofacial structures in normal subjects and patients with sleep apnea. Sleep 2014; 37:1689.
**11.** de Paula LK, Alvim RO, Pedrosa RP, et al. Heritability of OSA in a Rural Population. Chest 2016; 149:92.
**12.** Billings ME, Gold D, Szpiro A. The Association of Ambient Air Pollution with Sleep Apnea: The Multi-Ethnic Study of Atherosclerosis. Ann Am ThoracSoc 2019; 16:363.
**13.** Riaz S, Bhatti H, Sampat PJ, Dhamoon A. The Converging Pathologies of Obstructive Sleep Apnea and Atrial Arrhythmias. Cureus 2020; 12:e9388.
**14.** Nokes B, Raza H, Malhotra A. Pulmonary hypertension and obstructive sleep apnea. J Clin Sleep Med 2020; 16:649.
**15.** Fan ZQ, Lu XX, Long H, Li TP, Zhang YH. The association of hemocyte profile and obstructive sleep apnea. J. Clin. Lab. Anal. 2019;33:e22680.
**16.** Suri J, Suri JC, Arora R. The Impact of Sleep-Disordered Breathing on Severity of Pregnancy-Induced Hypertension and Feto-Maternal Outcomes. J ObstetGynaecol India 2019; 69:111.
**17.** Wu ZH, Yang XP, Niu X. The relationship between obstructive sleep apnea hypopnea syndrome and gastroesophageal reflux disease: a meta-analysis. Sleep Breath 2019; 23:389.
**18.** Kim J, Keenan BT, Lim DC, et al: Symptom-based subgroups of Koreans with obstructive sleep apnea. J Clin Sleep Med 14(3):437–443, 2018.
**19.** Myers KA, Mrkobrada M, Simel DL. Does this patient have obstructive sleep apnea?: The Rational Clinical Examination systematic review. JAMA 2013; 310:731.
**20.** Kunisaki KM, Greer N, Khalil W. Provider Types and Outcomes in Obstructive Sleep Apnea Case Finding and Treatment: A Systematic Review. Ann Intern Med 2018; 168:195.
**21.** Kapur VK, Auckley DH, Chowdhuri S, et al. Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An American Academy of

Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med 2017; 13:479.

**22.** Tarraubella N, Sánchez-de-la-Torre M, Nadal N. Management of obstructive sleep apnoea in a primary care vs sleep unit setting: a randomised controlled trial. Thorax 2018; 73:1152.

**23.** American Academy of Sleep Medicine. International Classification of Sleep Disorders, 3rd ed, American Academy of Sleep Medicine, 2014.

**24.** Wittine LM, Olson EJ, Morgenthaler TI. Effect of recording duration on the diagnostic accuracy of out-of-center sleep testing for obstructive sleep apnea. Sleep 2014; 37:969.

**25.** Ho V, Crainiceanu CM, Punjabi NM, et al. Calibration Model for Apnea-Hypopnea Indices: Impact of Alternative Criteria for Hypopneas. Sleep 2015; 38:1887.

**26.** Vgontzas AN, Li Y, He F, et al. Mild-to-moderate sleep apnea is associated with incident hypertension: age effect. Sleep 2019; 42.

**27.** Won CHJ, Qin L, Selim B, Yaggi HK. Varying Hypopnea Definitions Affect Obstructive Sleep Apnea Severity Classification and Association With Cardiovascular Disease. J Clin Sleep Med 2018; 14:1987.

**28.** Anttalainen U, Tenhunen M, Rimpilä V, et al. Prolonged partial upper airway obstruction during sleep - an underdiagnosed phenotype of sleep-disordered breathing. EurClinRespir J 2016; 3:31806.

**29.** Tenhunen M, Elomaa E, Sistonen H, et al. Emfit movement sensor in evaluating nocturnal breathing. RespirPhysiolNeurobiol 2013; 187:183.

**30.** Keenan BT, Kirchner HL, Veatch OJ, et al: Multisite validation of a simple electronic health record algorithm for identifying diagnosed obstructive sleep apnea. J Clin Sleep Med 16(2):175–183, 2020.

**31.** McEvoy RD, Antic NA, Heeley E, et al: CPAP for prevention of cardiovascular events in obstructive sleep apnea. N Engl J Med 375(10):919–931, 2016.

**32.** Baptista PM, Costantino A, Moffa A.Hypoglossal nerve stimulation in the treatment of obstructive sleep apnea: Patient selection and new perspectives. Nat Sci Sleep 12:151-159, 2020.

**33.** Miller JN, Kupzyk KA, Zimmerman L, et al. Comparisons of measures used to screen for obstructive sleep apnea in patients referred to a sleep clinic. Sleep Med 2018; 51:15.

**34.** Chen YH, Keller JK, Kang JH, et al. Obstructive sleep apnea and the subsequent risk of depressive disorder: a population-based follow-up study. J Clin Sleep Med 2013; 9:417.

**35.** Qaseem A, Dallas P, Owens DK, et al. Diagnosis of obstructive sleep apnea in adults: a clinical practice guideline from theAmerican College of Physicians. Ann Intern Med 2014; 161:210.

**36.** Jonas DE, Amick HR, Feltner C, et al. Screening for Obstructive Sleep Apnea in Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA 2017; 317:415.

**37.** Mertoglu C, Gunay M. Neutrophil-lymphocyte ratio and platelet-lymphocyte ratio as useful predictive markers of prediabetes and diabetes mellitus. Diabetes Metab. Syndr. 2017;11(Suppl 1):S127–S131.

**38.** Naess A, Nilssen SS, Mo R, Eide GE, Sjursen H. Role of neutrophil to lymphocyte and monocyte to lymphocyte ratios in the diagnosis of bacterial infection in patients with fever. Infection. 2017;45:299–307.

**39.** Howard R, Scheiner A, Kanetsky PA, Egan KM. Sociodemographic and lifestyle factors associated with the neutrophil-to-lymphocyte ratio. Ann. Epidemiol. 2019;38:11,e16–21 e16.

**40.** US Preventive Services Task Force, Bibbins-Domingo K, Grossman DC, et al. Screening for Obstructive Sleep Apnea in Adults: US Preventive Services Task Force Recommendation Statement. JAMA 2017; 317:407.

**41.** Hui DS, Ng SS, To KW, et al. A randomized controlled trial of an ambulatory approach versus the hospital-based approach in managing suspected obstructive sleep apnea syndrome. Sci Rep 2017; 8:45901.

**42.** Togeiro SM, Carneiro G, RibeiroFilho FF, et al. Consequences of obstructive sleep apnea on metabolic profile: a Population-Based Survey. Obesity (Silver Spring) 2013; 21:847.