Natural Resources for Human Health
eISSN: 2583-1194

Review Article

Received 05 Aug 2026
Revised 08 Sep 2026
Accepted 25 Sep 2026

Natural Resources for Human Health 2026, Vol. 6 (23s): 525–536

KEYWORDS:
Obstructive sleep apnoea; Biomarkers; Artificial intelligence; Machine learning; Polysomnography.

Beyond the Apnoea–Hypopnoea Index: Biomarkers and Artificial Intelligence in Obstructive Sleep Apnoea

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ABSTRACT: Obstructive sleep apnoea is one of the most prevalent sleep-related breathing disorders and is associated with significant cardiovascular, metabolic and neurocognitive morbidity. Although the apnoea–hypopnoea index remains an important measure for diagnosis and severity classification, increasing evidence suggests that it inadequately reflects the biological heterogeneity, symptom burden and long-term clinical outcomes of Obstructive sleep apnoea. Consequently, there is growing interest in complementary approaches that extend beyond conventional polysomnographic metrics. This review examines emerging non-invasive biomarkers and artificial intelligence approaches that may complement conventional physiological assessment of Obstructive sleep apnoea. Evidence relating to inflammatory, oxidative stress, metabolic and molecular biomarkers, together with emerging salivary and exhaled breath biomarkers, is critically reviewed, with particular attention to heterogeneity, confounding factors, diagnostic performance and current clinical readiness. The review also examines machine learning, deep learning and explainable artificial intelligence, with emphasis on model performance, validation, generalisability and the distinction between proof-of-concept performance and demonstrated clinical utility. Furthermore, opportunities and challenges associated with biomarker standardisation, clinical validation and implementation into routine practice are discussed. Although biomarker–Artificial Intelligence integration may provide complementary information on physiological burden, biological phenotype, risk and treatment response, most approaches remain investigational and require standardisation, external validation and prospective demonstration of clinical utility before routine implementation.

1. INTRODUCTION

Obstructive sleep apnoea (OSA) is a major global health concern with increasing prevalence due to rising obesity and sedentary lifestyles [1]. The disorder is characterised by recurrent partial or complete upper-airway obstruction during sleep, resulting in intermittent hypoxaemia, recurrent arousals, sympathetic activation and sleep fragmentation. Individuals with OSA may complain of tiredness, excessive day-time sleepiness, insomnia, or morning headaches, but many are asymptomatic [1]. These disturbances contribute to hypertension, insulin resistance, cardiovascular disease, and neurocognitive impairment [2, 3]. The most important epidemiological risk factors for Obstructive sleep apnoea Syndrome (OSAS) are obesity and male gender [4, 5]. OSAS plays an important role in the emergence and maintenance of hypertension, while snoring is a risk factor for hypertension independent of body mass index (BMI), Apnoea hypopnea index AHI, or older age [6].

The main metric for diagnosing OSA is the Apnoea hypopnea index (AHI). This reflects the average number of significant breathing disturbances per hour of sleep and is measured during Polysomnography (sleep study) which remains the 'gold-

standard' of diagnosis. [1]. Despite its clinical importance, OSA remains underdiagnosed due to reliance on polysomnography (PSG), which is resource-intensive and not universally accessible [1,2].

Although the AHI remains an important measure for diagnosing and grading OSA severity, increasing evidence indicates that it does not fully capture disease heterogeneity. In particular, AHI does not directly account for event duration, depth and duration of oxygen desaturation, cumulative hypoxaemic burden, arousal responses, or the influence of rapid eye movement (REM) sleep and body position. Night-to-night variability and differences in hypopnoea scoring criteria may further affect its interpretation. Consequently, complementary measures such as oxygen desaturation index (ODI), time spent with oxygen saturation below a defined threshold (T90), hypoxic burden and arousal-related metrics have been proposed to provide additional information on physiological burden. The AHI has limited ability to reflect the physiological mechanisms responsible for the neurocognitive, metabolic, and cardiovascular consequences of OSA. Its predictive value is constrained by three major factors: its inability to accurately represent the true pathophysiological burden of OSA due to measurement variability and scoring inaccuracies; inter-individual differences in susceptibility influenced by factors such as genetics, age, obesity, medications, and comorbidities; and the contribution of non-OSA factors to clinical outcomes, which limits the extent to which OSA severity alone can predict adverse events [7], highlighting the need for complementary approaches that better characterise disease activity and prognosis.

Although numerous candidate biomarkers have demonstrated potential for improving the diagnosis, risk assessment, and therapeutic monitoring of OSA, none has yet been established as an ideal biomarker for routine clinical use. Owing to the multifactorial nature of OSA, different biomarkers or biomarker panels may reflect distinct pathophysiological processes, including oxidative stress, intermittent hypoxia, inflammation, and sympathetic activation. In this context, classical serum-derived inflammatory and hematologic markers, composite lipid indices, pro-inflammatory cytokines and metabolic biomarkers such as adipokines, indices of insulin resistance (IR), and oxidative stress markers have been explored as candidate markers of biological activity, disease phenotype, risk and treatment response. However, many candidate biomarkers are influenced by obesity, ageing, metabolic disease, cardiovascular comorbidity and other inflammatory conditions, limiting their specificity for OSA. Consequently, integrated biomarker profiling may provide complementary information by capturing multiple biological processes, although evidence that multimarker approaches improve clinical prediction beyond established clinical and sleep-study variables remains limited. Furthermore, advances in proteomics and other high-throughput omics technologies are expected to facilitate the discovery and validation of novel biomarkers, thereby supporting future precision-based approaches to OSA diagnosis and management [8].

Parallel advances in artificial intelligence (AI) and machine learning have expanded opportunities for improving the diagnosis and management of OSA. AI-based analytical approaches can integrate polysomnographic signals with clinical, physiological and potentially biomarker data to support disease detection, phenotyping and risk prediction. [9]. However, performance reported in retrospective or selected datasets does not necessarily translate into clinical utility, and external validation, calibration, generalisability and prospective evaluation remain important requirements. As these technologies continue to evolve, they have the potential to complement conventional AHI-based assessment and support a more comprehensive and personalised approach to patient evaluation.

This review summarises current evidence on blood, salivary, breath and molecular-based biomarkers and examines how emerging AI technologies complement conventional diagnostic approaches in OSA. It highlights the potential of integrating biomarkers with computational methods to improve diagnosis, risk stratification, disease monitoring, and personalised management beyond reliance on the AHI alone.

Recent advances in OSA research have expanded the evaluation of individual biomarkers towards integrated multi-omics approaches, breathomics, and AI-assisted analytical models. Emerging biosensor technologies and machine learning algorithms have also been explored for real-time biomarker detection and the development of point-of-care diagnostic tools, although reported diagnostic performance requires validation across larger and more diverse populations [10, 11]. Despite these advances, clinical translation remains limited by lack of standardization and validation across populations. This highlights the need for integrated, validated diagnostic frameworks and prospective multicenter studies.

This review examines how complementary physiological measures, emerging biomarkers and artificial intelligence may extend conventional AHI-based assessment of OSA. Particular emphasis is placed on the strength and limitations of current evidence,

potential applications in diagnosis, phenotyping, risk prediction and treatment response, and the barriers that currently limit clinical translation.

2. LITERATURE SEARCH STRATEGY

A structured literature search was conducted to identify relevant studies on biomarkers and artificial intelligence (AI) in obstructive sleep apnoea (OSA). Electronic databases including PubMed/MEDLINE, Scopus, and Web of Science were searched for articles published between January 2015 and June 2026, with additional landmark studies included where considered scientifically relevant. The search was performed using combinations of the following keywords and Medical Subject Headings (MeSH): *"obstructive sleep apnoea" OR "obstructive sleep apnea"*, *"apnoea–hypopnoea index" OR "apnea–hypopnea index"*, "*Beyond the AHI*", *"biomarkers"*, *"blood biomarkers"*, *"salivary biomarkers"*, *"breath biomarkers"*, *"oxidative stress"*, *"inflammation"*, *"artificial intelligence"*, *"machine learning"*, *"deep learning"*, *"explainable artificial intelligence"*, *"precision medicine"*, and *"risk stratification"*.

Original research articles, systematic reviews, meta-analyses, and clinical practice guidelines published in English were considered. Studies focusing on biomarker discovery, AI-assisted diagnosis, disease phenotyping, risk prediction, treatment monitoring, and personalised management of OSA were prioritised. Reference lists of selected publications were also screened to identify additional relevant articles. Conference abstracts, editorials, non-English publications, animal studies, and studies lacking sufficient methodological detail were excluded. The final selection was based on scientific relevance, methodological quality, and clinical applicability to the objectives of this educational review.

3. PATHOPHYSIOLOGICAL BASIS FOR BIOMARKERS IN Obstructive Sleep ApnOea

OSA is characterized by recurrent upper-airway obstruction, intermittent hypoxemia, sleep fragmentation, recurrent arousals, and sympathetic activation, which may contribute to oxidative stress, systemic inflammation, metabolic dysregulation, and vascular dysfunction [3, 8]. Intermittent hypoxemia can increase the generation of reactive oxygen species (ROS) and activate inflammatory pathways such as NF-κB, with subsequent alterations in cytokine production and endothelial function [3]. ROS may react with nucleic acids, proteins, and lipids, contributing to cellular damage and inflammatory responses. Recurrent hypoxemia and sympathetic activation may also promote metabolic disturbances and platelet activation [12]. These biological responses provide a rationale for investigating circulating and non-circulating biomarkers as potential indicators of physiological and molecular changes associated with OSA. However, many of these pathways are not specific to OSA and may also be influenced by obesity, metabolic disease, cardiovascular disease, and other comorbid conditions.

4. SERUM BIOMARKERS IN Obstructive Sleep ApnOea

The growing recognition of its systemic inflammatory profile has shifted research interest toward identifying blood-based biomarkers that reflect disease severity and treatment response.

4.1 Inflammatory markers

Serum inflammatory markers such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and high-sensitivity C-reactive protein (hs-CRP) have been reported at higher levels in OSA patients [2]. These markers may be associated with disease severity and systemic inflammation, although their diagnostic specificity remains limited.

Systemic inflammation is increasingly implicated in the pathophysiology of OSA. Inflammatory markers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and Fibrinogen have previously been linked to OSA. Furthermore, derived hematological indices such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and the systemic immune-inflammation index (SII) have emerged as accessible, cost-effective markers that capture immune imbalance and hypercoagulability—two key features in the OSA inflammatory phenotype. Despite existing evidence, the biomarkers that best reflect OSA severity or treatment response remain unclear, as prior studies often lacked sufficient sample size, robust design, or severity-based analysis [11].

Although inflammatory biomarkers may correlate with disease severity, their clinical utility is limited by relatively low specificity. Similar inflammatory profiles may occur in obesity, metabolic syndrome, cardiovascular disease, and other chronic inflammatory conditions. A systematic review and meta-analysis of peripheral biomarkers in adults with OSA also highlighted substantial heterogeneity across studies and concluded that biomarker research remains at an early stage [13]. Therefore, these markers should currently be considered complementary indicators rather than standalone diagnostic biomarkers.

4.2 Oxidative stress markers

Biomarkers of oxidative stress have the potential to be used to assess disease severity and treatment response. Markers including malondialdehyde (MDA) and superoxide dismutase (SOD) reflect oxidative imbalance associated with intermittent hypoxia.

Superoxide dismutase (SOD) is an important antioxidant enzyme involved in the removal of reactive oxygen species. Lower SOD activity has been reported in patients with OSA compared with healthy subjects [14]. A recent study also reported an association between oxidative stress biomarkers and increasing OSA severity [15]. These findings suggest that oxidative stress markers may provide additional information regarding disease burden, although their clinical utility remains to be established.

MDA is a marker of lipid peroxidation and has been investigated as an indicator of oxidative stress in OSA. A systematic review and meta-analysis reported significantly higher circulating MDA concentrations in patients with OSA compared with non-OSA controls [16]. However, heterogeneity among studies and potential confounding factors limit the interpretation of MDA as an OSA-specific biomarker.

Larger longitudinal studies are required before these biomarkers can be incorporated into routine clinical practice.

4.3 Metabolic biomarkers

OSA is frequently associated with metabolic dysfunction. Biomarkers such as leptin, adiponectin, and insulin resistance indices have therefore been investigated in affected individuals [17]. Of the adipokines, leptin and adiponectin have received considerable attention.

Leptin concentrations are generally elevated in obesity, whereas adiponectin levels tend to be lower in obesity and metabolic dysfunction [18–20]. Because obesity is a major risk factor for OSA and independently influences adipokine concentrations, the independent association of these biomarkers with OSA remains difficult to establish. Consequently, adipokines may be more useful as components of a broader biomarker profile than as standalone diagnostic markers.

Although combining metabolic and inflammatory biomarkers may be promising, evidence demonstrating improved diagnostic performance over individual biomarkers remains limited. Serum biomarkers should therefore be interpreted in the context of obesity, metabolic status, and other relevant comorbidities.

4.4. Emerging biomarkers

Circulating cell-free DNA (cfDNA) are extracellular fragments of DNA present in body fluid that may be derived from both normal and diseased cells. Cell-free DNA (cfDNA) has gained attention as a marker of cellular damage and disease severity. High cell free-DNA (cfDNA) levels are considered a serum marker of many inflammatory diseases, such as stroke, ischemic heart failure, acute coronary syndrome, and OSA [21]. Free radicals in OSA patients destroy nucleic acids and lead to a higher level of free nucleosomes and cfDNA. The levels of cfDNA were found to be significantly higher in OSA patients compared with healthy subjects [22]. Moreover, a linear correlation between cfDNA concentration and severity of disease was observed [23].

Intermittent hypoxia associated with obstructive sleep apnoea is often associated with cardiac, metabolic, and neoplastic alterations. A large number of studies in recent years have demonstrated that microRNAs play an essential role in the pathogenesis of obstructive sleep apnoea and offer considerable potential as a critical new target for the diagnosis and management of patients with this disease. MicroRNAs (miRNAs) are small non-coding RNA molecules that play an important role in RNA silencing and regulation of gene expression at the post-transcriptional level. These can bind specifically to their target genes by forming silencing complexes, thus inducing degradation or altered gene expression [24].

Recent studies revealed that expression patterns of specific microRNAs are associated with OSA development and progress. In particular, a study by Santamaria-Martos et al. showed that patients with OSA exhibit a dysregulated miRNA profile compared to non-OSA patients [25]. In this regard, it appears that intermittent hypoxia, associated with OSA, may lead to differential expression of some hypoxia-induced miRNAs. This evidence suggests the importance of miRNAs and the pathways regulated by them. An alteration in their expression could result in a deregulation of key genes and pathways that contribute to the development and progression of OSA.

Overall, although several circulating biomarkers show differences between patients with OSA and controls and some demonstrate changes following treatment, the available evidence remains heterogeneous and is limited by methodological

variability and risk of bias. An umbrella review of meta-analyses identified several potentially useful inflammatory, metabolic, and oxidative stress biomarkers but emphasized the generally low quality of the underlying evidence [26].

5. SALIVARY BIOMARKERS

Saliva contains proteins, metabolites, DNA, and microbial components and has been investigated as a non-invasive source of biomarkers with the potential for convenient sampling [27, 28]. Among the salivary biomarkers studied in OSA are cortisol and pro-inflammatory cytokines.

Salivary cortisol has been investigated as a potential indicator of hypothalamic-pituitary-adrenal axis activity in OSA. However, a meta-analysis found no significant difference in morning salivary cortisol concentrations between adults with and without OSA, indicating that its diagnostic value in adults remains uncertain [29].

Salivary inflammatory biomarkers, including interleukin-6 (IL-6), interleukin-33 (IL-33), and tumor necrosis factor-alpha (TNF-α), have also been investigated in patients with OSA. Some studies have reported associations between salivary inflammatory biomarkers and OSA, whereas findings have been inconsistent. Differences in saliva collection and processing methods may contribute to this variability [27, 28].

Interpretation of salivary biomarkers may also be influenced by oral and periodontal health and changes in the oral microbial environment. In patients with OSA, salivary inflammatory markers have been studied in relation to periodontal disease, further highlighting the potential for oral inflammatory factors to influence biomarker measurements [30]. Therefore, salivary biomarkers should currently be considered potential adjunctive indicators rather than alternative diagnostic tests for OSA. Standardized collection and analytical protocols, together with larger prospective studies, are required to establish their diagnostic performance and clinical utility [28].

6. BREATH BIOMARKERS

Exhaled breath analysis is a non-invasive approach that has been investigated for identifying metabolic and inflammatory signatures associated with OSA. Its potential advantages include relatively simple sample collection and the possibility of rapid analysis; however, the diagnostic value of breath biomarkers remains investigational and is influenced by analytical and biological variability [31].

6.1 Volatile Organic Compounds (VOCs)

Volatile organic compounds (VOCs) are low-molecular-weight chemicals present in exhaled breath that may reflect endogenous metabolic processes as well as exogenous exposures. In OSA, breath metabolomics studies have identified differences in VOC patterns between patients with OSA and control participants, suggesting potential utility for screening and phenotyping. A 2025 study using proton-transfer-reaction mass spectrometry (PTR-MS) identified differences in breath VOC profiles between individuals with OSA and controls, supporting further investigation of breath-based biomarkers. [32]

However, VOC profiles are not necessarily specific to OSA. Smoking, age, body mass index (BMI), and sex can influence breath VOC profiles, as demonstrated in a large population-based study [33]. Diet, medication use, environmental exposures, and coexisting respiratory conditions may also affect breath composition and should be considered potential confounders in OSA studies. Differences in breath collection procedures, sampling of mixed versus end-tidal breath, storage conditions, analytical platforms, and data-processing methods may further contribute to variability between studies. Importantly, evidence from validation studies illustrates the gap between discovery and clinical utility. In an independent validation cohort of 149 participants with possible OSA, breath biomarkers identified using secondary electrospray ionization high-resolution mass spectrometry showed significant differences between OSA and non-OSA groups; however, a classification model trained on a previous cohort achieved an area under the receiver operating characteristic curve (AUC) of only 0.66 in the independent cohort. The authors therefore suggested that breath analysis may have value as an objective screening approach but emphasized the need for further evaluation, including assessment in combination with established screening tools [34].

Electronic-nose approaches have also demonstrated promising preliminary diagnostic performance. In an early study of 40 patients with OSA and 20 healthy controls, an electronic-nose model achieved an AUC of 0.85 (95% CI 0.75–0.96), with a sensitivity of 0.93 and specificity of 0.70. However, the small sample size and limited validation restrict the generalizability of these findings [35].

Overall, breath VOCs should currently be regarded as candidate biomarkers rather than disease-specific diagnostic markers. Larger prospective studies with independent external validation, standardized sampling and analytical protocols, and careful control of smoking, diet, obesity, medications, environmental exposures, and respiratory comorbidities are required before breath VOC analysis can be considered for routine OSA diagnosis.

6.2 Exhaled Nitric Oxide

Nitric oxide (NO) is involved in airway signaling and inflammation, and reactive nitrogen species may contribute to oxidative and inflammatory processes in the respiratory tract. These biological pathways provide a rationale for investigating exhaled NO in OSA [36].

Studies have reported alterations in exhaled or airway-derived NO in patients with OSA; however, the findings are not sufficiently consistent to establish exhaled NO as a standalone diagnostic biomarker. Increased oral NO has also been reported in OSA, but oral and upper-airway sources should be distinguished from lower-airway exhaled NO measurements when interpreting these findings [37].

Exhaled breath analysis has also been investigated in relation to treatment. Some studies have reported changes in breath profiles following continuous positive airway pressure (CPAP) therapy, suggesting that breath biomarkers may reflect biological or metabolic changes associated with treatment. However, changes in a breath biomarker should not be equated with CPAP adherence, and evidence remains insufficient to establish breath analysis as an objective measure of treatment adherence or treatment response [38].

Overall, breath biomarkers, including VOCs and exhaled NO, remain promising but experimental approaches. Their clinical translation will require standardized sampling and analytical procedures, reproducible biomarker signatures, adequately powered prospective studies, and external validation in representative populations.

Summary of Biomarkers in Obstructive sleep apnoea is given in Table 1

Biomarker Type	Examples	Mechanism	Clinical Utility
Inflammatory	IL-6, TNF-α	Systemic inflammation	Severity
Oxidative	MDA, SOD	ROS imbalance	Monitoring
Metabolic	Leptin and Adiponectin	Insulin resistance	Risk stratification
Genetic	miRNA, cfDNA	Gene regulation	Early detection
Breath	VOCs, FeNO	Metabolic signature	Non-invasive diagnosis

CfDNA, Cell-free DNA; FeNO, Fractional Exhaled Nitric Oxide; IL-6, Interleukin-6; MDA, Malondialdehyde; miRNA, MicroRNA; SOD, Superoxide Dismutase; TNF-α, Tumor Necrosis Factor-alpha; VOC, Volatile Organic Compound.

7. INTEGRATED BIOMARKER PROFILING

Obstructive sleep apnea (OSA) is a heterogeneous disorder, and individual biomarkers may capture only specific aspects of its pathophysiology. Integrated biomarker profiling offers a potential approach to combining information from serum, saliva, and exhaled breath with clinical characteristics and sleep-study findings. Such integration may help characterize disease heterogeneity more comprehensively; however, improved diagnostic accuracy cannot be assumed without direct comparative evaluation and independent validation.

Precision medicine research in OSA has also explored the integration of circulating biomarkers with symptom patterns, polysomnographic phenotypes, and physiological endotypes to better characterize patient subgroups [39, 40]. Although these approaches may eventually support risk stratification and more individualized treatment decisions, their prognostic value and clinical utility require further investigation in well-designed prospective studies.

The integration of heterogeneous biomarker and clinical datasets also presents analytical challenges, including differences in measurement methods, confounding factors, missing data, and the need for reproducible validation. Computational approaches,

including artificial intelligence, may help identify patterns across these datasets. Nevertheless, the clinical relevance of such models depends on their performance in independent populations and their ability to improve decisions beyond established clinical assessments.

8. ARTIFICIAL INTELLIGENCE IN OBSTRUCTIVE SLEEP APNOEA

OSA is a heterogeneous disorder. Patients with similar AHI values often differ markedly in symptom burden, cardiovascular risk, physiological traits, and treatment response. Conventional analyses based on polysomnography and clinical parameters may fail to capture this complexity.

The American Academy of Sleep Medicine (AASM) emphasizes the need for AI applications to optimize sleep diagnostics. AI-assisted PSG analysis is feasible, demonstrating concurrence with manual scoring and indicates efficiency improvements. Recent advances in Artificial Intelligence (AI), including Machine Learning (ML) and deep learning (DL) algorithms, offer novel potential tools for an accurate OSA screening and diagnosis. AI-based models have shown promising performance in OSA screening and detection; however, reported performance varies across datasets, study designs, and validation methods, and superiority over conventional approaches cannot be assumed across all settings. In particular, anthropometric indexes were most widely used, especially in logistic regression-powered algorithms. The application of AI algorithms to OSA diagnosis and screening has great potential to improve patient outcomes, increase early detection, and lessen the load on healthcare systems. However, further validation is needed to improve a better evaluation accuracy for each single parameter and standardization efforts must be made to standardize datasets.

8.1 *Machine Learning for Obstructive Sleep Apnoea Diagnosis and Severity Prediction*

To develop an automated machine learning model for OSA diagnosis, severity prediction, and treatment-response, five advanced algorithms used on patients who underwent polysomnography include [41]:

Random Forest

Support Vector Machine (SVM)

Extreme Gradient Boosting (XGBoost)

Light Gradient Boosting Machine (LightGBM)

Logistic Regression

These models were used using following predictor variables:

Demographic data

Anthropometric measurements

Medical history and

Epworth Sleepiness Scale (ESS) scores

Among the evaluated predictors, body mass index (BMI) and the total Epworth Sleepiness Scale (ESS) score were identified as the most influential variables, highlighting their importance in the clinical assessment of OSA [41].

Compared with conventional statistical approaches, ML models can capture nonlinear relationships among variables and identify combinations of features associated with OSA diagnosis or severity. However, predicting diagnosis or severity alone does not establish physiological endotypes, which require characterization of underlying physiological traits.

8.2 *Deep Learning Approaches*

Deep learning enables automated feature extraction without extensive manual engineering.

Two recent studies evaluated advanced artificial intelligence approaches for the automated detection and classification of sleep apnoea (SA) using physiological signals. The study by Patnaik, B et al proposed a hybrid deep learning framework based on single-lead electrocardiogram (ECG) recordings from the PhysioNet Apnoea-ECG dataset, integrating comprehensive signal preprocessing and feature engineering to improve the morphological and temporal representation of ECG signals. The

performance of conventional machine learning models, including Support Vector Machine (SVM) with linear, polynomial, sigmoid, and radial basis function (RBF) kernels, was compared with deep learning architectures such as one-dimensional convolutional neural networks (1D-CNN), 1D-CNN–bidirectional long short-term memory (1D-CNN–BiLSTM), and a hybrid 1D-CNN + BiLSTM incorporating an attention mechanism. The attention module enabled the model to emphasize diagnostically relevant temporal ECG segments, thereby enhancing feature representation and improving sleep apnoea detection [42].

Another study by M. Faisal et al compared the performance of four deep learning architectures—1D convolutional neural network (CNN1D), CNN–LSTM, bidirectional long short-term memory (BiLSTM), and Transformer—for classifying sleep apnea subtypes using time-series physiological data. Model performance was assessed using classification accuracy, confusion matrix analysis, and training time. Among the evaluated models, the Transformer achieved the highest classification accuracy (94.5%), outperforming BiLSTM (92.8%), CNN–LSTM (91.2%), and CNN1D (89.7%). Although CNN1D exhibited the shortest training duration, the Transformer required slightly longer computational time while providing the greatest diagnostic accuracy and the least inter-class misclassification [43]. Collectively, these findings demonstrate the potential of deep learning architectures for automated sleep-apnea detection and classification. However, the reported performance should be interpreted in the context of the datasets and validation methods used. Independent external validation, assessment across heterogeneous populations, and evaluation of class imbalance and calibration are needed before generalizability to routine clinical practice can be established.

8.3 *Artificial Intelligence-Assisted Polysomnography*

Traditionally, sleep staging and apnoea–hypopnea event scoring from polysomnography (PSG) recordings are performed manually by sleep technologists, making the process time-consuming and susceptible to inter-scorer variability. AI algorithms automate this analysis by accurately recognizing patterns in airflow, oxygen desaturation, and sleep stages. Some AI-based models have reported high performance in detecting sleep-related events from PSG recordings [9]. However, event-level detection accuracy is distinct from patient-level diagnostic performance, which requires separate evaluation against an appropriate diagnostic reference standard.

8.4 *Artificial Intelligence for Biomarker Integration*

One of the most promising applications of AI is the integration of molecular biomarkers with physiological and clinical data. AI can identify biomarker combinations that may outperform individual markers for predicting disease severity, cardiovascular risk, or treatment response.

Aliyeva et al. evaluated the diagnostic and prognostic significance of systemic inflammatory markers, including C-reactive protein (CRP), the systemic immune-inflammation index (SII), and fibrinogen, in patients with obstructive sleep apnoea syndrome (OSAS). The study also developed a machine learning model to classify disease severity and predict treatment outcomes. Among the biomarkers, CRP exhibited the greatest diagnostic performance for identifying severe OSAS, whereas fibrinogen demonstrated the strongest association with disease severity and the most pronounced reduction following therapy. SII was likewise significantly correlated with polysomnographic (PSG) severity and showed a marked decline after treatment. Machine learning analyses identified CRP, SII, and fibrinogen as the most influential predictors of OSAS severity, while clustering analysis distinguished three inflammatory endotypes characterized by distinct biomarker profiles and treatment responses [11]. This multimodal approach is aligned with the goals of precision medicine by moving beyond single-variable assessment.

8.5 *Predicting Treatment Response*

Although continuous positive airway pressure (CPAP) is an established treatment for OSA, adherence may be limited by discomfort or difficulties with pressure settings. Automatic positive airway pressure (APAP) devices adjust delivered pressure in response to detected breathing patterns using control algorithms, many of which are conventional rule-based systems rather than artificial intelligence models [9].

8.6 *Explainable Artificial Intelligence*

A major limitation of many AI models is their "black-box" nature. Though the automated sleep apnea identification algorithms have received a lot of recognition and have illustrated positive outcomes in identifying SA based on physiological signals, there

is one noticeable gap: the uninterpretable nature of machine learning. The blackbox aspect of machine learning approaches, typically taking an input, generating an outcome, and not explaining the model's conclusion, is one of the main causes of concern. The explainable artificial intelligence approach provides insights into the inside mechanisms and outcomes provided by machine learning algorithms. XAI techniques are broadly categorized into ante-hoc and post-hoc approaches. Ante-hoc methods emphasize the development of inherently interpretable models, such as rule-based algorithms, that can explain their reasoning during the prediction process. In contrast, post-hoc methods are applied after model training to interpret and explain the outputs generated by otherwise complex or opaque algorithms. These techniques may improve the interpretability of complex AI models by explaining the factors contributing to their predictions. However, interpretability alone does not establish diagnostic reliability, clinical utility, or generalizability across populations [44].

This study gives an approach for diagnosing sleep apnea using explainable AI methods applied to single-lead ECG readings. The process includes extracting features from ECG readings and using models such as Multilayer Perceptron (MLP), Support Vector Machine (SVM), Gradient Boosting (GB), and Long Short-Term Memory (LSTM) networks to detect apnea events. Explainable Artificial Intelligence (XAI) techniques, such as Decision Trees and Local Interpretable Model-agnostic Explanations (LIME), enhance the transparency of machine learning models by providing insights into their decision-making process. Experimental results demonstrated that the proposed models effectively identified apnea episodes from time-windowed ECG signals in the Apnea-ECG database with high accuracy. Incorporating LIME can help identify the features contributing to model predictions and improve transparency. However, the reported performance on the Apnea-ECG database does not, by itself, establish clinical reliability or generalizability to independent patient populations [44].

AI demonstrates significant promise in the diagnosis and management of OSA. Future clinical application hinges on developing large-scale standardized datasets, enhancing model explainability, and conducting robust clinical validation.

9. PREVENTIVE MEDICINE IMPLICATIONS

The integration of biomarkers with artificial intelligence has the potential to shift the management of obstructive sleep apnoea (OSA) from a predominantly reactive approach to one focused on prevention and early intervention. Biomarkers reflecting inflammation, oxidative stress, metabolic dysfunction, and tissue injury may facilitate the early identification of individuals at increased risk of OSA, particularly among those with obesity, metabolic syndrome, or other cardiometabolic risk factors. When combined with artificial intelligence algorithms capable of integrating biomarker profiles with clinical and physiological data, these approaches may improve risk prediction, disease stratification, and identification of patients most likely to develop adverse cardiovascular or metabolic complications.

Earlier recognition of high-risk individuals could enable timely interventions, including lifestyle modification, weight management, continuous positive airway pressure (CPAP) therapy, or other personalised treatment strategies before irreversible organ damage occurs. Furthermore, serial assessment of biomarkers together with AI-assisted monitoring may provide an objective means of evaluating treatment response and disease progression, supporting more precise and proactive patient management. Although further validation and standardisation are required before routine clinical implementation, the combination of biomarker profiling and AI represents an important step towards preventive, personalised, and precision medicine in OSA.

10. LIMITATIONS

Current evidence on biomarkers in obstructive sleep apnoea is limited by significant heterogeneity in study design, population characteristics, and analytical methodologies. Many studies are based on small sample sizes and lack external validation, reducing generalizability. In addition, variability in biomarker measurement techniques and absence of standardized diagnostic thresholds hinder comparability across studies. Furthermore, most biomarkers lack disease specificity due to overlap with other inflammatory and metabolic conditions.

11. FUTURE DIRECTIONS

Future research should focus on large-scale, multicentre studies to validate promising biomarkers across diverse populations. The development of standardized protocols for biomarker collection and analysis is essential to ensure reproducibility and clinical applicability. Integration of multi-omics technologies with advanced computational approaches, including artificial intelligence, may enable the identification of robust biomarker signatures. Additionally, efforts should focus on translating these findings into cost-effective, user-friendly diagnostic tools suitable for routine clinical practice and large-scale screening.

12. CONCLUSION

Although no single biomarker currently fulfills the requirements for routine clinical application, integrating multimodal biomarkers with artificial intelligence may complement conventional physiological assessment and support a more biologically informed, personalised approach to OSA, pending further clinical validation. Future multicentre validation studies and standardized analytical protocols will be essential before these technologies can be translated into routine respiratory practice.

Ethical permission

No ethics approval was required as this study did not involve the collection of new data from human participants or laboratory animals.

Funding: No funding was received for this work

Conflict of interest: No Conflict of interest

CONTRIBUTOR: The author solely conceived the idea, performed the literature review and drafted the manuscript.

REFERENCES

[1] Chamara V. Senaratna, Jennifer L. Perret, Caroline J. Lodge, Adrian J. Lowe, Brittany E. Campbell, Melanie C. Matheson, Garun S. Hamilton, Shyamali C. Dharmage. Prevalence of obstructive sleep apnea in the general population: A systematic review. Sleep Med Rev. 2017, Volume 34; 70-81. DOI: 10.1016/j.smrv.2016.07.002

[2] Graziela De Luca Canto, Camila Pachêco-Pereira, Secil Aydinoz, Paul W. Major, Carlos Flores-Mir, David Gozal. Biomarkers associated with obstructive sleep apnea: a scoping review. Sleep Med Rev. 2014, Volume 23; 28-45. DOI: 10.1016/j.smrv.2014.11.002

[3] Unnikrishnan D, et al. Oxidative stress and inflammation in obstructive sleep apnea. Biomedicines. 2023, 11(5):1471. DOI: 10.3390/biomedicines11051471.

[4] Davies R. The relationship between neck circumference, radiographic pharyngeal anatomy, and the obstructive sleep apnoea syndrome. Eur Respir J (1990) 3:509–14.

[5] Reichmuth KJ, Austin D, Skatrud JB, Young T. Association of sleep apnea and type II diabetes: a population-based study. Am J Respir Crit Care Med (2005) 172:1590–5. doi: 10.1164/rccm.200504-637OC

[6] Khazaie H, Negahban S, Ghadami MR, Sadeghi Bahmani D, Holsboer-Trachsler E, Brand S. Among middle-aged adults, snoring predicted hypertension independently of sleep apnoea. J Int Med Res (2018) 46:1187–96. doi: 10.1177/0300060517738426

[7] Malhotra A, Ayappa I, Ayas N, Collop N, Kirsch D, Mcardle N, Mehra R, Pack AI, Punjabi N, White DP, Gottlieb DJ. Metrics of sleep apnea severity: beyond the apnea-hypopnea index. Sleep. 2021 Jul 9;44(7): zsab030. doi: 10.1093/sleep/zsab030. PMID: 33693939; PMCID: PMC8271129.

[8] Kheirandish-Gozal L, Gozal D. Biomarkers of obstructive sleep apnea. Current Opinion in Pulmonary Medicine. 2019;25(6):594–600. DOI: 10.1097/MCP.0000000000000623

[9] Surya Prakash Bhatt, Amisha Khurana. Artificial intelligence in obstructive sleep apnea: Transforming diagnosis and management. Respiratory Medicine, Volume 243, 2025, 108100. ISSN 0954-6111. https://doi.org/10.1016/j.rmed.2025.108100.

[10] Guo L, Zhao Y, Huang Q, et al. Electrochemical protein biosensors for disease marker detection: progress and opportunities. Microsystems & Nanoengineering. 2024;10:65. DOI: 10.1038/s41378-024-00700-w

[11] Aliyeva, A.; Hashimli, R.; Yılmaz, B. Hematological Biomarkers of the Obstructive Sleep Apnea Syndrome: A Machine Learning-Based Diagnostic and Prognostic Model. J. Clin. Med. 2025, 14, 8437. https://doi.org/10.3390/jcm14238437

[12] Stanek A, Brożyna-Tkaczyk K, Myśliński W. Oxidative Stress Markers among Obstructive Sleep Apnea Patients. Oxidative Medicine and Cellular Longevity; Jul 19; 2021:9681595. doi: 10.1155/2021/9681595. PMID: 34336121; PMCID: PMC8321764.

[13] Gaspar LS, Santos-Carvalho A, Santos B, et al. Peripheral biomarkers to diagnose obstructive sleep apnea in adults: systematic review/meta-analysis. Sleep Med Rev. 2022;64:101659. doi:10.1016/j.smrv.2022.101659.

[14] E. Wysocka, S. Cofta, M. Cymerys, J. Gozdzik, L. Torlinski, and H. Batura-Gabryel, "The impact of the sleep apnea syndrome on oxidant-antioxidant balance in the blood of overweight and obese patients," Journal of Physiology and Pharmacology, vol. 59, Supplement 6, 761–769, 2008.

[15] Karthik Nagaraju, Kavitha Venkatnarayan, Chitra Veluthat, Uma Devaraj, Priya Ramachandran, Uma Maheswari Krishnaswamy. Evaluation of Oxidative Stress Biomarkers and Their Correlation with Severity of Obstructive Sleep Apnea. Indian Journal of Sleep Medicine, Volume 20 Issue 2 (April–June 2025) 48-51.
[16] Pau MC, Zinellu E, Fois SS, Piras B, Pintus G, Carru C, Mangoni AA, Fois AG, Zinellu A, Pirina P. Circulating Malondialdehyde Concentrations in Obstructive Sleep Apnea (OSA): A Systematic Review and Meta-Analysis with Meta-Regression. Antioxidants (Basel). 2021 Jun 29;10(7):1053. doi: 10.3390/antiox10071053. PMID: 34210032; PMCID: PMC8300833.
[17] Lam DCL, Lam KSL, Ip MSM. Obstructive sleep apnoea, insulin resistance and adipocytokines. Clinical Endocrinology. 2015;82(2):165–177.DOI: 10.1111/cen.12597
[18] Heymsfield SB, Greenberg AS, Fujioka K, et al. Recombinant leptin for weight loss in obese and lean adults: a randomized, controlled, dose-escalation trial. JAMA 282 (16): 1568-1575, 1999.
[19] Considine RV, Sinha MK, Heiman ML, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med 334 (5): 292-295, 1996.
[20] Hotta K, Funahashi T, Arita Y, et al. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. Arterioscler Thromb Vasc Biol 20 (6): 1595-1599, 2000.
[21] N. W. Tsai, T. K. Lin, S. D. Chen et al., "The value of serial plasma nuclear and mitochondrial DNA levels in patients with acute ischemic stroke," Clinica Chimica Acta, vol. 412, no. 5–6, pp. 476–479, 2011.
[22] J. M. Bauça, A. Yañez, L. Fueyo et al., "Cell death biomarkers and obstructive sleep apnea: implications in the acute coronary syndrome," Sleep, vol. 40, no. 5, 2017.
[23] L. Ye, G.-H. Ma, L. Chen et al., "Quantification of circulating cell-free DNA in the serum of patients with obstructive sleep apnea-hypopnea syndrome," Lung, vol. 188, no. 6, pp. 469– 474, 2010.
[24] Moriondo, G.; Soccio, P.; Tondo, P.; Scioscia, G.; Sabato, R.; Foschino Barbaro, M.P.; Lacedonia, D. Obstructive Sleep Apnea: A Look towards Micro-RNAs as Biomarkers of the Future. Biology 2023, 12, 66. https://doi.org/10.3390/biology12010066.
[25] Santamaria-Martos, F.; Benítez, I.; Ortega, F.; Zapater, A.; Giron, C.; Pinilla, L.; Pascual, L.; Cortijo, A.; Dalmases, M.; Fernandez-Real, J.M.; et al. Circulating microRNA profile as a potential biomarker for obstructive sleep apnea diagnosis. Sci. Rep. 2019, 9, 13456. [CrossRef] [PubMed]
[26] Fiedorczuk P, Polecka A, Walasek M, Olszewska E. Potential Diagnostic and Monitoring Biomarkers of Obstructive Sleep Apnea—Umbrella Review of Meta-Analyses. J Clin Med. 2023;12(1):60. doi:10.3390/jcm12010060.
[27] Chuan-Xiang Li, Liu Zhang, Ya-Ru Yan, Yong-Jie Ding, Ying-Ni Lin, Jian-Ping Zhou, Ning Li, Hong-Peng Li, Shi-Qi Li, Xian-Wen Sun, Qing-Yun Li. A narrative review of exploring potential salivary biomarkers in respiratory diseases: still on its way. Journal of Thoracic Disease 2021;13(7):4541-4553 | http://dx.doi.org/10.21037/jtd-21-202.
[28] Bencharit S, Redenz RG, Brody ER, Chiang H. Salivary biomarkers associated with obstructive sleep apnea: a systematic review. Expert Rev Mol Diagn. 2021;21(2):223–233. doi:10.1080/14737159.2021.1873132.
[29] Imani MM, Sadeghi M, Khazaie H, Sanjabi A, Brand S, Brühl A and Sadeghi Bahmani D (2021) Associations Between Morning Salivary and Blood Cortisol Concentrations in Individuals With Obstructive Sleep Apnea Syndrome: A Meta-Analysis. Front. Endocrinol. 11:568823. doi: 10.3389/fendo.2020.568823.
[30] Téllez Corral MA, Daza EH, Jimenez NA, Morales Vera DZ, Velosa Porras J, Latorre Uriza C, Escobar Arregoces FM, Martinez PH, Cortés ME, Otero L, Parra Giraldo CM, Roa Molina NS. Biomarkers for the severity of periodontal disease in patients with obstructive sleep apnea:IL-1 β, IL-6, IL-17A, and IL-33. Heliyon. 2023 Mar 14;9(3):e14340. doi: 10.1016/j.heliyon.2023.e14340. PMID: 36967976; PMCID: PMC10031375.
[31] Sharma, A.; Kumar, R.; Varadwaj, P. Smelling the disease: Diagnostic potential of breath analysis. Mol. Diagn. Ther. 2023, 27, 321–347. Doi:10.1007/s40291-023-00640-7 [CrossRef] [PubMed]
[32] Gui, C.H.; Jia, Z.; Xing, Z.; Zhang, F.; Du, F.; Tham, A.C.; Lim, M.Y.; Chong, Y.K.; Chew, A.S.Q.; Chong, K.B. A Study of Volatile Organic Compounds in Patients with Obstructive Sleep Apnea. Metabolites 2025, 15, 42. https://doi.org/10.3390/ metabo15010042.
[33] Blanchet L, Smolinska A, Baranska A, Tigchelaar-Feenstra E, Swertz MA, Zhernakova A, Dallinga JW, Wijmenga C, van Schooten FJ. Factors that influence the volatile organic compound content in human breath. J Breath Res. 2017;11(1):016013. doi:10.1088/1752-7163/aa5cc5.
[34] Nora Nowak, Anna Engler, Sira Thiel, Anna S. Stoberl, Pablo Sinues, Renato Zenobi, Malcolm Kohler. Validation of breath biomarkers for obstructive sleep apnea. Sleep Medicine 85 (2021) 75-86.
[35] Greulich T, Hattesohl A, Grabisch A, et al. Detection of obstructive sleep apnoea by an electronic nose. Eur Respir J. 2013;42(1):145–155. doi:10.1183/09031936.00091712.

[36] Bove PF, van der Vliet A. Nitric oxide and reactive nitrogen species in airway epithelial signalling and inflammation. Free Radic Biol Med 2006;41(4):515e27.
[37] Culla B, Guida G, Brussino L, Tribolo A, Cicolin A, Sciascia S, Badiu I, Mietta S, Bucca C. Increased oral nitric oxide in obstructive sleep apnoea. Respir Med. 2010;104:316–320.
[38] Schwarz EI, Engler A, Kohler M. Exhaled breath analysis in obstructive sleep apnea. Expet Rev Respir Med 2017;11:631e9. https://doi.org/10.1080/ 17476348.2017.1338950.
[39] Liu Y, Abdul Ghafoor A, Hajipour M, Ayas N. Role of precision medicine in obstructive sleep apnoea. BMJ Medicine. 2023;2:e000218. https://doi.org/10.1136/bmjmed-2022-000218
[40] Edwards BA, Redline S, Sands SA, Owens RL. More than the sum of the respiratory events: personalized medicine approaches for obstructive sleep apnea. Am J Respir Crit Care Med. 2019;200(6):691–703. doi:10.1164/rccm.201901-0014TR.
[41] Liu K, Geng S, Shen P, Zhao L, Zhou P, Liu W. Development and application of a machine learning-based predictive model for obstructive sleep apnea screening. Front in Big Data. 2024 May 16;7:1353469. doi: 10.3389/fdata.2024.1353469. PMID: 38817683; PMCID: PMC11137315.
[42] Patnaik, B., Nayak, D.S.K. & Sahoo, S. Attention enhanced hybrid deep learning model with 1D-CNN and BiLSTM for automated sleep apnea detection. Discov Appl Sci 7, 1376 (2025). https://doi.org/10.1007/s42452-025-07639-1
[43] M. Faisal, A. K. Baghmar, K. Lahkar and R. Gupta, "Evaluating Multi-Modality Deep Learning Models for Automated Sleep Apnea Detection," 2025 International Conference on Sensors and Related Networks (SENNET) Special Focus on Digital Healthcare(64220), Vellore, India, 2025, pp. 1-6, doi: 10.1109/SENNET64220.2025.11136079.
[44] Jyoti Gupta, Seeja K.R. An Explainable AI Approach Towards Automatic Sleep Apnea Detection Based on ECG Signal, Procedia Computer Science, Volume 258, 2025, Pages 937-946, ISSN 1877-0509, https://doi.org/10.1016/j.procs.2025.04.332.