POLITECNICO DI TORINO

Master's Degree in Biomedical Engineering

Master's Degree Thesis

Evaluation of a New Feature to Predict Long-Term Adherence to Continuous Positive Airway Pressure Treatment in Obstructive Sleep Apnea Syndrome Patients

Supervisors
Dr. Marco GHISLIERI
Prof. Elena MUGELLINI

Candidate
Benedetta GIACHETTI
s314284

October 2024

Summary

Obstructive Sleep Apnea Syndrome (OSAS) is a prevalent and significant disorder characterized by repeated episodes of partial or complete upper airway obstruction during sleep. It can lead to fragmented sleep, excessive daytime sleepiness, and various long-term health complications, including cardiovascular diseases and metabolic disorders. The disorder is primarily diagnosed through nocturnal polysomnography, which provide objective data on the frequency and severity of respiratory events. However, while Continuous Positive Airway Pressure (CPAP) therapy remains the gold standard for managing moderate-to-severe OSAS, non-adherence to the therapy remains a critical challenge. Despite its effectiveness, less than half of patients achieve sufficient adherence to CPAP therapy, which is defined as at least four hours of nightly use.

The clinical challenge of managing OSAS lies in the overwhelming number of patients who need continuous monitoring to ensure adherence to treatment. CPAP telemonitoring systems are used to track usage and detect potential issues, but they generate a substantial amount of data, leading to information overload for clinicians. This raises the need for a more streamlined, targeted approach to identify which patients are likely to experience poor adherence and to focus on interventions that could improve their treatment outcomes.

The hypothesis underlying this study is that CPAP adherence is significantly influenced by psycho-behavioral factors, particularly in terms of how consistently a patient uses the device over time. This variability in adherence, or the monthly variance in CPAP usage, could serve as an important predictor of long-term treatment outcomes. The aim of this research is to investigate whether a single variable, the monthly variance in adherence (VarAdh), can stratify patients into subgroups with distinct patterns of adherence and long-term outcomes. By doing so, it would allow clinicians to focus their attention on patients who are most at risk of non-adherence or ineffective therapy.

In this study, the potential of the VarAdh variable to serve as a predictive marker

of CPAP adherence is examined. The analysis is focused on telemonitoring data collected from a large population of OSAS patients over three separate months (January, June, December). The methodology includes the clustering of patients based solely on their adherence variance, with the goal of identifying clusters that can differentiate between patients with differing adherence behaviors and clinical outcomes.

The results of this study demonstrate the predictive potential of the VarAdh variable in identifying long-term CPAP adherence patterns. In particular, a Pearson correlation coefficient of -0.32 between VarAdh in January and monthly mean adherence (MeanAdh) in December indicates that higher variance in early adherence is associated with significantly lower long-term adherence. Furthermore, the positive Pearson correlation of 0.39 between VarAdh and days without CPAP use per month (NullAdh) underscores the role of adherence variance as a predictor of device non-use. Both correlations are statistically significant, with p-values below 5%, confirming the robustness of these findings.

The significance of this study lies in its potential to enhance the management of OSAS by providing clinicians with a simple, yet powerful, predictive marker that can help target interventions more effectively.

Acknowledgements

ACKNOWLEDGMENTS

Table of Contents

List of Tables

List of Figures

Acronyms

AI
Artificial Intelligence

SBD
Sleep-Related Breathing Disorder

CSAS
Central Sleep Apnea Syndrome

OSAS
Obstructive Sleep Apnea Syndrome

HSAT
Home Sleep Apnoea Test

ICSD
International Classification of Sleep Disorders

AHI
Apnea-Hypopnea Index

REI
Respiratory Event Index

ODI
Oxygen Desaturation Index

RDI
Respiratory Disturbance Index

ESS

Epworth Sleepiness Scale

EDS

Excessive Daytime Sleepiness

T90

Time below 90% Oxygen Saturation

HB

Hypoxic Burden

ORP

Odds Ratio Product

EEG

Electroencephalogram

PAP

Positive Airway Pressure

CPAP

Continuous Positive Airway Pressure

MAD

Mandibular Advancement Device

TRD

Tongue-Retaining Device

HGNS

Hypoglossal Nerve Stimulation

EHR

Electronic Health Record

JA

January

JU

June

DE

December

VarAdh

Monthly Variance of Adherence (hours)

MeanAdh

Monthly Mean of Adherence (hours)

MeanLeaks

Monthly Mean of Leaks (L/min)

MeanAhi

Monthly Mean of AHI (events/hour)

CC

Combined Criterion

NullAdh

Number of Nights with Null Adherence per Month

ROC

Receiver Operating Characteristic

AUC

Area Under the Curve

Chapter 1

Introduction

1.1 Definition of OSAS

Sleep-related Breathing Disorder (SBD) is a term used to describe a spectrum of respiratory disturbances that occur during sleep [1].
The International Classification of Sleep Disorders (ICSD) has defined the two major categories of SBD: central sleep apnea syndrome (CSAS) and obstructive sleep apnea syndrome (OSAS) [2].

The fundamental difference between the major categories is the pathophysiologic mechanism causing the respiratory disturbance. CSAS involves dysfunction of ventilatory control in the central nervous system (loss of ventilatory effort); in OSAS, the upper airway obstruction is most often caused by abnormal anatomy and/or abnormal control of the muscles that maintain the patency of the upper airway [1].

OSAS is characterized by discrete episodes of partial or complete airway collapse during sleep, despite respiratory effort. It is diagnosed based on night-time symptoms (sleep-related breathing disturbances: snoring, snorting, gasping, or breathing pauses) and daytime symptoms (excessive daytime sleepiness, fatigue unexplained by sufficient sleep opportunity or other medical problems), as well as objective data from a home sleep apnoea test (HSAT) or polysomnography study [3]. Further details are discussed about the tests in section 1.2.

In order to gain a deeper understanding of the underlying causes of this disorder, it is vital to undertake a detailed examination of the anatomy of the upper airways, as their structure has a significant impact on the maintenance of airway patency.

1.1.1 Anatomy

Upper airway obstruction during sleep often results from negative collapsing pressure during inspiration. Additionally, progressive expiratory narrowing in the retropalatal area significantly contributes to this condition. The extent of upper airway narrowing during sleep correlates with body mass index, highlighting the roles of anatomical and neuromuscular factors in airway obstruction [4].
The airway consists of the organs that facilitate airflow during ventilation: from the nares and buccal opening to the blind end of the alveolar sacs. The airway is categorized into the upper and lower airway, with each category having further subdivisions. This division ensures the respiratory system efficiently manages the intake of oxygen and expulsion of carbon dioxide, supporting essential physiological processes.
The **upper airway** includes critical structures that play essential roles in respiration and speech production (figure 1.1). It spans from the base of the skull to the esophagus and comprises the following subdivisions:

- Nasopharynx: Also known as the rhino-pharynx or post-nasal space, the nasopharynx is a muscular tube that extends from the nares, encompassing the posterior nasal cavity. It is separated from the oropharynx by the palate and lined superiorly by the base of the skull.

- Oropharynx: Connecting the nasopharynx and hypopharynx, the oropharynx is situated between the palate and the hyoid bone. It is anteriorly divided from the oral cavity by the tonsillar arch, serving as a pathway for both air and food.

- Hypopharynx: This portion links the oropharynx to the esophagus and the larynx. Located below the hyoid bone, the hypopharynx directs the passage of air to the lower respiratory tract and food to the esophagus.

- Larynx: Positioned between the pharynx and the trachea, the larynx contains the organs responsible for speech production. Its cartilaginous structure is made up of nine cartilages, including the epiglottis and vocal folds (vocal cords), which regulate airflow and protect the airway during swallowing by closing the glottis [5].

Current investigations into the pathophysiologic mechanisms of OSAS are exploring various factors, including a structural susceptibility to upper airway collapse, heightened ventilatory control instability (loop gain), lower arousal threshold, dysfunctional upper airway dilator muscles or hypoglossal nerve activity, reduced lung tethering, and nocturnal rostral fluid shift. Additionally, ongoing research

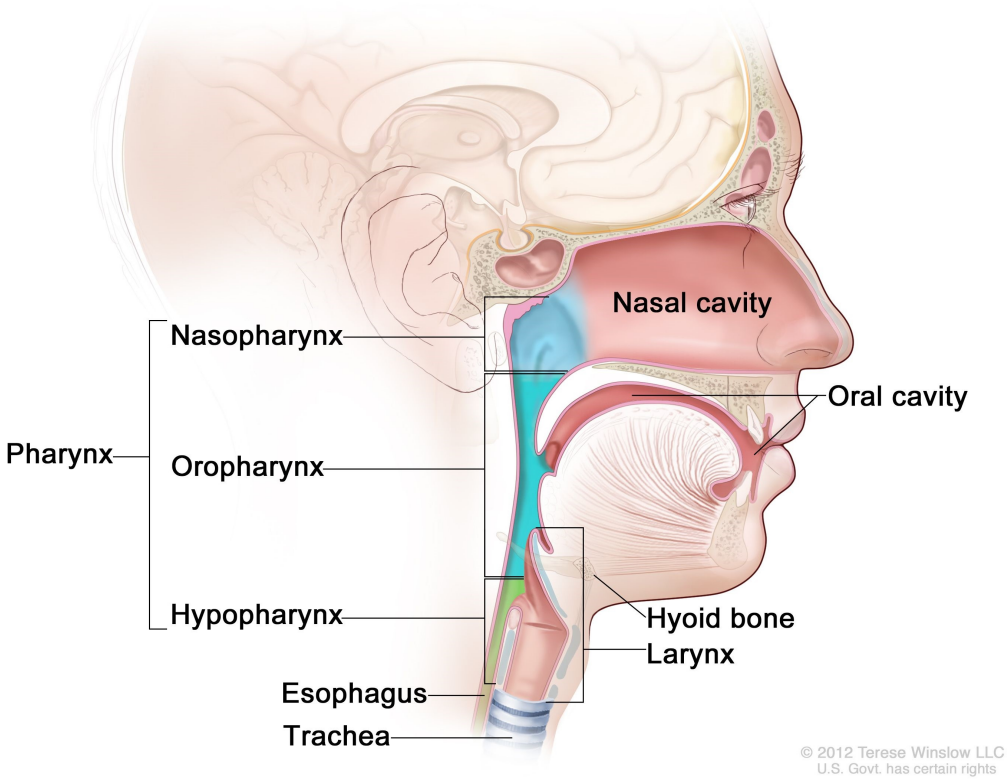


Figure 1.1: Anatomy of the upper airway [6].

aims to identify biomarkers and genetic determinants that could predict negative outcomes linked to OSAS [7, 8].
Given the intimate relationship between the anatomical structure and the onset of the respiratory disorder, we will now proceed to examine the principal diagnostic modalities, including polysomnography and HSAT, which facilitate the assessment of the extent of this pathology.

1.2 Diagnosis tests for OSAS

Accurate diagnosis of OSAS is crucial for effective treatment and management. This section provides an overview of the primary diagnostic tests used to evaluate OSAS, namely polysomnography and home sleep apnea testing (HSAT). The choice between these tests depends on various factors, including the patient's condition and the clinical context.

1.2.1 Polysomnography

Polysomnography is an in-depth sleep test that usually takes place in a hospital lab or off-site sleep clinic. It involves the collection of seven or more data channels:

- Electroencephalogram (EEG) and electrooculogram (EOG) for sleep staging,
- Electromyogram (EMG),
- Electrocardiogram (ECG),
- Respiratory channels.

It is the gold standard for the diagnosis of OSAS. Polysomnography is particularly important when patients are at risk of CSAS or hypoventilation [9]. This test is also recommended for evaluating suspected sleep disorders other than OSAS or when HSAT is inconclusive in patients with a high pretest probability of OSA [10].

The figure 1.2 shows 5 possible signals that can be extracted from the polysomnography test from a patient who suffer from severe OSAS. It's possible to notice the airflow pattern which is marked by frequent episodes where the airway becomes partially or fully blocked (A), the patterns of movements between the chest and abdomen are often (B) and intrathoracic pressure is characterized by significant fluctuations (C). These respiratory disruptions cause intermittent reductions in oxygen levels (D), result in awakenings from sleep (A), and trigger increases in heart rate (E) [3].

1.2.2 Home sleep apnea testing

HSAT records a minimum of three channels of data while the patient sleeps at home. This test usually monitors:

- Airflow,
- Snoring,
- Respiratory excursion,
- Body position,
- Heart rate,
- Oxygen saturation,
- Surrogate measurements [11].

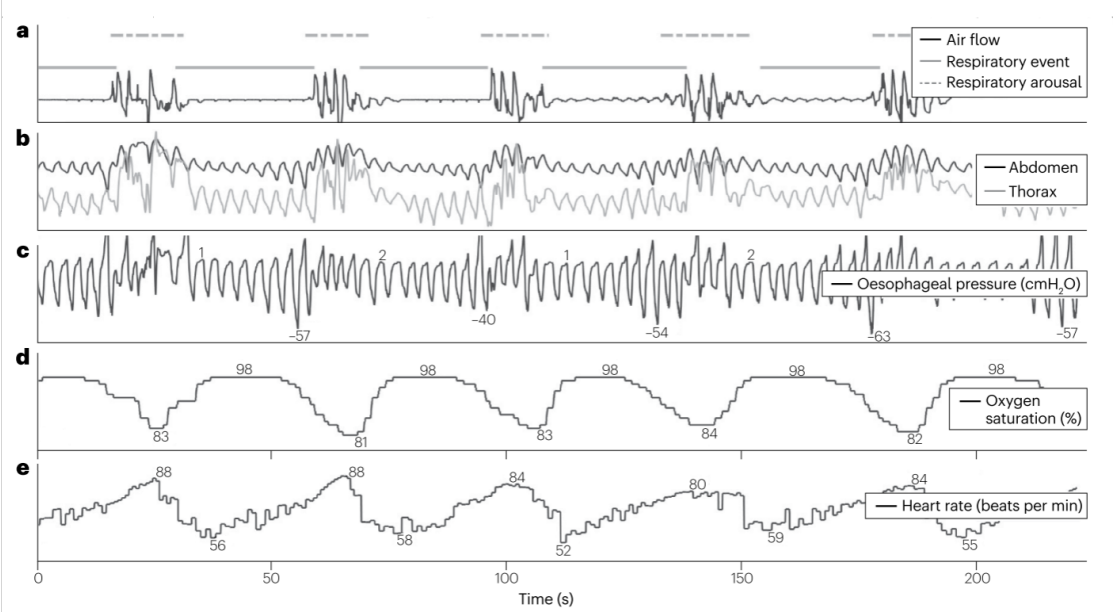


Figure 1.2: Polysomnographic features of severe OSAS: (A) obstructions of the airway and arousals from sleep; (B) out-of-phase movements of the thorax and abdomen; (C) large intrathoracic pressure swings; (D) intermittent drops in oxygen saturation; (E) surges in heart rate [3].

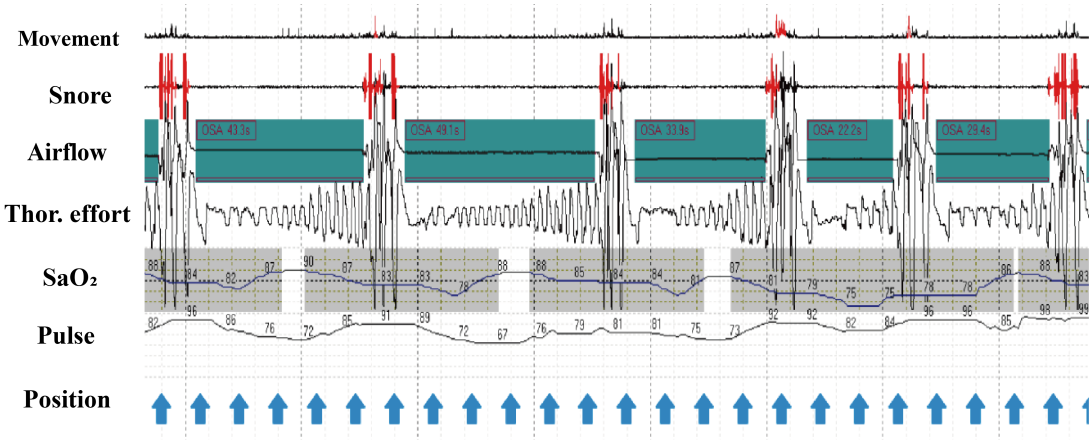


Figure 1.3: HSAT traces: - movement, - snore, - airflow, - thoracic effort, - oxygen saturation, - pulse, - position [12].

The figure 1.3 shows examples of signals that can be extracted from the patient during an HSAT test [12].

The main differences between polysomnography and HSAT are the cost (HSAT is

much more cost-effective), the location where the test is conducted, the accuracy (polysomnography is much more accurate), and the recording of sleep (HSAT does not record sleep). This last difference leads to another consequential difference: the extractable metric. During polysomnography, the Apnea-Hypopnea Index (AHI) can be determined, whereas during HSAT, the Respiratory Event Index (REI) is measured [3]. These metrics are explored in depth in Section 1.3 where there are more details about them.
Although HSATs are commonly used due to their lower cost, laboratory-based polysomnography is used to evaluate patients with complex comorbidities, including heart failure [3].
In Table 1.1, one can find a comprehensive tabulation of the diagnostic criteria for OSAS, to facilitate the understanding of the parameters and thresholds used in the diagnosis of this condition.
Table 1.2 provides a classification of the severity of OSAS based on the AHI. The severity is categorized mainly into three levels: mild, moderate, and severe. This classification helps in determining the appropriate treatment and management strategies for patients with sleep apnea.
After reviewing the diagnostic methods, it is crucial to understand how the results obtained from these tests are translated into severity metrics.

1.3 Severity metrics

- AHI:
  Apnoea–hypopnoea index is defined as the number of obstructive respiratory events (apnoea[1] and hypopnoea[2]) per hour of sleep, recorded with polysomnography [3].

$$\text{AHI} = \frac{\text{apnoeas} + \text{hypopnoeas}}{\text{hours of sleep}} \tag{1.1}$$

- REI:
  Respiratory event index is defined as the number of obstructive respiratory events (apnoea[1] and hypopnoea[2]) per hour of estimated sleep, recorded with a HSAT [3].

$$\text{REI} = \frac{\text{apnoeas} + \text{hypopnoeas}}{\text{hours of estimated sleep}} \tag{1.2}$$

[1]Apnoea: complete or nearly complete reduction in airflow lasting $\geq$ 10 s each.

[2]Hypopnoea: reductions $\geq$ 30% in airflow for $\geq$ 10 s, accompanied by an oxygen desaturation or a respiratory arousal[4].

A	**The presence of one or more of the following:** • The patient reports sleepiness, nonrestorative sleep, fatigue, or insomnia symptoms. • The patient wakes with breath holding, gasping, or choking. • The bed partner or other observer reports habitual snoring, breathing interruptions, or both during the patient's sleep. • A diagnosis of hypertension, a mood disorder, cognitive dysfunction, coronary artery disease, stroke, congestive heart failure, atrial fibrillation, or type 2 diabetes mellitus in the patient. **AND:** Five or more predominantly obstructive respiratory events per hour of sleep during polysomnography or per hour of monitoring during HSAT.
B	**Polysomnography or HSAT shows:** • Fifteen or more predominantly obstructive respiratory events per hour of sleep during polysomnography or per hour of monitoring during HSAT.

Table 1.1: Diagnosing obstructive sleep apnea: A or B satisfy the criteria for a diagnosis of OSAS [3, 13].

Severity	**Events per hour (AHI)**
Mild	$5 \leq \text{AHI} \leq 14$
Moderate	$15 \leq \text{AHI} \leq 30$
Severe	$\text{AHI} > 30$

Table 1.2: Severity of sleep apnea based on AHI [10].

When interpreting the results of HSATs, it is crucial to understand that they can underestimate the AHI through REI by about 12%, with even greater underestimation occurring in cases of poor sleep quality. Therefore, patients with a high

pre-test probability of OSAS who receive a negative result from a home study should undergo further evaluation [14].

New techniques for quantifying overnight hypoxemia, sleep fragmentation, diagnosing, and assessing OSAS have demonstrated prognostic value that surpasses standard summary sleep metrics.

- ODI:
  Oxygen Desaturation Index refers to the average number of desaturation episodes[3] occurring per hour [15].

- RDI:
  Respiratory Disturbance Index accounts for respiratory effort-related arousals[4] in addition to apnoea and hypopnoea [9].

- ESS:
  The Epworth Sleepiness Scale (ESS) is a widely used tool for assessing the general level of daytime sleepiness in individuals. The scale consists of 8 questions or scenarios. Each question describes a different activity, such as watching TV, sitting and reading, or sitting in a public place, and asks how likely the person is to fall asleep during that activity. Respondents rate their likelihood of falling asleep in each situation on a scale from 0 to 3. The scores for each of the 8 items are summed to produce a total score ranging from 0 to 24. An ESS score > 10 suggests excessive daytime sleepiness (EDS) [16].

- T90:
  Time Below 90% Oxygen Saturation measures the total amount of time that a patient's oxygen saturation level drops below 90% throughout the entire sleep period [17].

- HB:
  The Hypoxic Burden is defined as the sum of individual areas under the oxygen desaturation curve. In addition to the frequency of respiratory events, HB captures the depth and duration of OSAS-related hypoxemia, not captured by the conventional "frequency-based" metrics, such as AHI and ODI [18].

- ORP:
  The Odds Ratio Product is a continuous measure of sleep depth developed

[3]Desaturation episodes: decrease in the mean oxygen saturation of $\geq 3\%$ (over the last 120 seconds) that lasts for at least 10 seconds.

[4]Respiratory effort-related arousals: brief awakenings that occur after a change in breathing.

using spectral analysis from the Fourier transform of EEG signals. It evaluates the relative power in different EEG frequency ranges (delta, theta, alpha/sigma, and beta). The ORP is calculated for consecutive 3-second epochs [19].

- ORP-9:
  The Odds Ratio Product-9 is an index derived from the ORP, which is used to measure sleep drive. ORP-9 specifically averages the ORP value 9 seconds after an arousal or awakening. This metric reflects an individual's ability to return to sleep after an arousal; a lower ORP-9 indicates a quicker return to deeper sleep, whereas a higher ORP-9 suggests a higher susceptibility to repeated arousals or awakenings within the next 30 seconds [19].

These advanced metrics have the potential to modernize physiological biomarkers obtained from polysomnography or HSAT [19]. These biomarkers could be integrated with other types of data, such as omics data, questionnaires, genetic information, and imaging results, to provide a comprehensive understanding of sleep mechanisms and their impact on clinical outcomes.
Once the gravity of the disorder has been established, an investigation will be made into the available treatment options, which range from behavioural modifications to surgical interventions, to effectively address OSAS.

1.4 Therapies

Once the diagnosis of OSAS is established, an adequate treatment strategy should be decided. OSAS management typically involves behavioral modifications, positive airway pressure (PAP) device therapy, mouth appliances, mandibular advancement devices, supplement therapies, and surgeries in severe cases of OSAS.

1.4.1 PAP Therapies

PAP is a treatment for sleep apnea which uses a machine to help keep the patient's airways open while sleeping [9]. Types of PAP machines include CPAP (Continuous Positive Airway Pressure), Auto-Adjusting Positive Airway Pressure (APAP), Bilevel Positive Airway Pressure (BiPAP or BPAP), Adaptive Servo-Ventilation (ASV), Expiratory Positive Airway Pressure (EPAP). PAP devices are utilized to lower AHI values and are considered the primary treatment for managing OSAS. These devices are particularly effective for moderate-to-severe cases of OSAS. PAP machines come with a mask that is worn over the nose and mouth, or sometimes just under the nose, delivering pressurized air either continuously or intermittently during sleep. This increased air pressure prevents airway collapse, ensuring uninterrupted breathing and reducing sleep fragmentation.

Among all the different types of PAP devices, CPAP is the most frequently used. CPAP machines maintain a constant airway pressure during both inhalation and exhalation, achieved by a servo-controlled air compressor that adjusts the pressure to remain as close to the target level as possible, regardless of the patient's breathing pattern [20].

1.4.2 Oral Appliances

Oral appliances are suggested for patients with mild to moderate OSAS who either cannot tolerate CPAP or choose not to use it. These devices include mandibular advancement devices and tongue-retaining devices [9].
The mandibular advancement device (MAD) has demonstrated considerable effectiveness in treating snoring and OSAS. It is particularly beneficial for patients with mild-to-moderate sleep apnea and can also reduce bruxism (nocturnal grinding). Also referred to as mandibular repositioning appliances, MADs work by advancing the mandible forward, which alters the position of the tongue and mandible, thereby preventing upper airway collapse. The design features of MADs significantly influence their effectiveness in treating OSAS [20].
The tongue-retaining device (TRD) is a custom-made mouthpiece that pulls the tongue forward by creating negative pressure, helping to prevent airway obstruction. Its performance is comparable to mandibular advancement devices (MAD) and may be recommended as an alternative to CPAP for patients with nasal obstruction, though it is rarely used and primarily in Asia [21].

1.4.3 Surgery

Surgical treatment plans are tailored based on the anatomical sites of obstruction. Common procedures include nasal surgery, removal of excess tissue in the oropharynx, tongue surgeries, craniofacial surgery, tracheostomy.
Surgical interventions for the nasal cavity include procedures such as correcting a deviated septum, reducing inferior turbinates, reconstructing the alar valve, and performing sinus surgery if sinus issues are present. The primary aim of these surgeries is to enhance nasal airflow by addressing obstructive elements like a deviated septum or enlarged turbinates. Although the literature indicates that nasal surgery alone rarely provides a complete solution for OSAS, it has been shown to improve sleep quality. Additionally, nasal surgery can facilitate better adherence to CPAP therapy by reducing the required pressure and increasing the duration of CPAP use.
Oropharyngeal surgery's goal is to reduce the tissue excess and to increase the stiffness of the soft tissues in the area. Patients with OSAS often have excess tissue in the oropharynx, which is typically more lax and elongated.

Procedures targeting the tongue include either tongue reduction techniques or genioglossus muscle suspension methods. These procedures generally help alleviate daytime sleepiness and improve overall quality of life. In retrolingual region individuals with sleep apnea often have increased fat deposits in the tongue, resulting in an enlarged base. Additionally, lingual tonsil hypertrophy may be observed. The genioglossus muscle, which plays a key role in airway dilation, is affected in sleep apnea patients. Research has indicated that the tone of the genioglossus muscle in these individuals differs from that in healthy individuals during sleep.
A tracheostomy, which bypasses the upper airway, is the most effective surgical treatment for curing OSAS. However, patients with concurrent cardiopulmonary conditions such as chronic obstructive pulmonary disease, congestive heart failure, or obesity hypoventilation syndrome may still experience residual issues. A permanent tracheostomy requires daily care and should be considered only for carefully selected patients. In high-risk individuals, a temporary tracheostomy may be used as a precautionary measure before undergoing other airway surgeries [22].

1.4.4 Lifestyle changing

Behavioral interventions for OSAS include: weight loss, diet and exercise, smoking cessation, alcohol reduction and positional therapy
Reducing weight can significantly improve OSA by decreasing airway narrowing associated with obesity. Intensive weight loss programs, including very low-calorie diets and increased physical activity, have been shown to reduce OSAS severity and improve sleep parameters.
A balanced diet combined with regular exercise helps manage weight, which in turn reduces OSAS severity. Effective programs include healthy eating habits and consistent physical activity, leading to improvements in apnea-hypopnea index (AHI) and overall sleep quality.
Smoking exacerbates OSAS through airway inflammation and structural changes. Quitting smoking can alleviate OSAS symptoms and enhance treatment outcomes, as smoking cessation reduces the negative impacts on airway health.
Alcohol consumption worsens OSAS by increasing the frequency and duration of apnea episodes, particularly during the first few hours of sleep. Reducing or eliminating alcohol intake can improve OSAS severity and overall sleep quality.
Used as an alternative for patients intolerant to CPAP or those with positional OSAS, positional therapy involves techniques to prevent sleeping on the back. In some people with OSAS, airway collapse is worse when they sleep lying on their back, so sleeping on their side is preferable. There are positioning devices that can help people remain in an optimal position during sleep. Although effective in reducing AHI and daytime sleepiness, long-term compliance can be challenging

and requires regular follow-up.
These behavioral strategies, while beneficial, often need ongoing monitoring to ensure effectiveness and adherence [20].

1.4.5 Nerve Stimulation Treatment

Hypoglossal nerve stimulation (HGNS) is an alternative treatment for moderate-to-severe OSAS in patients who are either resistant to or cannot tolerate CPAP therapy. This surgical approach involves implanting a stimulator that is connected to the hypoglossal nerve, which controls the genioglossus muscle. Stimulation of this nerve prompts the muscle to contract, thereby preventing upper airway collapse. Research indicates that hypoglossal nerve stimulation notably enhances quality of life, reduces the AHI, and improves the ODI [23].

1.5 Adherence to CPAP

CPAP is termed the gold standard for therapy of OSA and indeed when used as prescribed, the health benefits are substantial. However, this modality of treatment continues to be plagued by problems with adherence [24]. Clinical trial results [25] indicate that less than half of patients continue using CPAP for more than four hours per night after one year. This level of usage may be crucial for achieving the full therapeutic benefits. Factors such as the severity of OSA, psychological considerations, and the management of CPAP-related side effects have all been linked to patient adherence to this treatment [26].
Patients in France are eligible to have CPAP prescribed if they have at least three clinical symptoms (see item 1.) and meet one of the AHI criteria (see item 2.).

1. **Clinical Symptoms** :
    - Daytime sleepiness;
    - Severe and daily snoring;
    - Sensations of choking during sleep;
    - Daytime fatigue;
    - Nocturia;
    - Morning headaches.
2. **AHI Criteria** :
    - AHI $\geq$ 30/h based on total sleep time during polygraphy or polysomnography;

- AHI $\geq$ 15/h and $<$ 30/h based on total sleep time during polygraphy or polysomnography with:
  - Severe daytime sleepiness and/or risk of accidents;
  - Severe cardiovascular or respiratory comorbidity (e.g., resistant hypertension, atrial fibrillation, symptomatic heart failure, coronary artery disease, history of stroke, severe COPD, or poorly controlled asthma) [26].

National french guidelines for CPAP reimbursement stipulate that patients must use the device for more than 4 hours per night to qualify for full reimbursement (adherence hours can be monitored through automatic data extraction from the device and telemonitoring explored in more depth in Section 1.5.1). Reimbursement rates decrease progressively with lower adherence levels. However, CPAP can still be delivered and reimbursed if the patient uses it between 2 and 4 hours per night, provided there is ongoing patient education and support. The final decision regarding the continuation of therapy, including the evaluation of adherence and perceived benefits, is determined by the treating physician, considering both patient and physician perspectives. Regular follow-up appointments are mandated, occurring 4 months after CPAP initiation and annually thereafter, to maintain reimbursement eligibility [26]. The current definition of adherence is largely arbitrary and is mainly used by third-party payers to determine CPAP reimbursement [27]. However, real-world data demonstrate a clear dose-response relationship between CPAP usage and healthcare resource utilization, with benefits observed even at 2–3 hours per night [28]. This treatment modality relies heavily on patient acceptance and adherence that's why strategies to augment adherence, especially early in the course of a CPAP trial, are needed in the management of OSAS.

1.5.1 Telemonitoring

The initial phase of CPAP therapy is crucial in determining long-term treatment adherence. It has been shown that low adherence at the beginning of treatment increases the risk of poor compliance or even discontinuation. Literature data and the recommendations of the American Academy of Sleep Medicine emphasize the importance of close monitoring during the first week to identify patients who may require intensive follow-up. Most of the CPAP devices currently in use allow telemonitoring of observance (compliance: daily duration of CPAP use in hours), leaks and the AHI.
The total **leak** rate is defined as the combination of intentional leaks (necessary to clear CO_2 from the circuit) and unintentional leaks. There is significant variability among manufacturers in how leaks are estimated and labeled (e.g., total leaks, unintentional leaks, 90/95th percentile leaks, median leaks, average leaks, etc.).

An excessive level of leaks is linked to an increased incidence of ear, nose, and throat (ENT) side effects (such as nasal obstruction, rhinorrhea, dry mouth, and headaches), sleep fragmentation, and potentially lower short-term adherence. Intermittent leaks are likely more harmful than continuous leaks. Therefore, leaks are categorized as either intentional or unintentional. Unintentional leaks are then further divided into continuous and intermittent leaks:

- A continuous unintentional leak primarily suggests an issue with the circuit, such as the tubing itself or the connections between the machine and the tubing, the tubing and the mask, or the mask and its cushion. The correct fit of the mask should then be checked on the patient in a lying position at therapeutic pressure (considering mask size and appropriate harness tightening). Less commonly, continuous unintentional leaks are caused by a slight, persistent mouth opening.
- In the case of intermittent unintentional leaks, it's important to first consider either a problem with the mask shifting during the patient's position changes or mouth openings.

CPAP devices' software calculates a **residual AHI**. Each manufacturer, and sometimes each model, employs distinct methods for detecting respiratory events. Definitions of apnea and especially hypopnea can vary between machine models, making inter-device comparisons challenging. These "manufacturer definitions" of events, which do not include measurements of oxygen desaturation or micro-arousals, differ inherently from those proposed by professional societies. Typically, machine software tends to overestimate the AHI when the polysomnographic AHI is low and underestimate it when the polysomnographic AHI is high. The correlation between machine-derived indices and PSG indices is considered acceptable for apneas but is significantly lower for hypopneas. However, manufacturers agree that high levels of leaks can impair the device's ability to accurately identify events. Although elevated AHI levels may not always align with polysomnographic events, they may have clinical significance that warrants careful monitoring. The main causes of residual obstructive events with CPAP can be:

- use of a full face mask: obstructive apneas primarily occur when lying on the back. If switching to a nasal mask is not possible due to significant mouth leaks, it is advisable to either sleep on the side or use a cervical collar. An ENT consultation is recommended to assess nasal obstruction causing mouth breathing.
- increased upper airway resistance: this can be due to chronic issues like nasal septum deviation or nasal obstruction, or transient factors such as viral infections, allergic rhinitis, or the use of sedatives, medications, or

alcohol. Heated humidification is beneficial for patients with rhinitis or nasal obstruction. Persistent nasal obstruction should be evaluated by an ENT specialist to determine the specific obstructive anomalies and potential allergic conditions.

– insufficient treatment pressure: this can occur with a prolonged pressure ramp or comfort modes that may lead to residual obstructive events during pressure drops.

– occurrence of residual events in clusters: this may indicate a connection with sleeping position (e.g., supine position) or REM sleep.

Identifying these events is important because they are associated with an increased risk of stopping treatment with CPAP [29].

1.5.2 Predictors - State of art

The adherence to CPAP therapy for OSAS is influenced by various factors that can enhance or impede consistent usage. Understanding these predictors is crucial for improving treatment adherence and, consequently, patient outcomes. This chapter summarizes the current state of the art regarding the predictors of adherence to CPAP therapy, drawing from recent literature.

Patient characteristics

Patient characteristics significantly influence adherence to CPAP therapy, although certain demographic factors such as age, sex, and marital status have not consistently shown a strong correlation with adherence levels [30].
Psychological traits also play a crucial role in adherence to CPAP therapy. Research has shown that Type D personality, characterized by negative affectivity and social inhibition, is prevalent in a significant portion of OSA patients and is associated with lower adherence rates and a higher likelihood of treatment discontinuation [31].
Perceptions of OSA symptoms and the risks associated with sleep-disordered breathing, along with expectations regarding treatment outcomes, self-efficacy, and coping strategies, are also critical. Patients who are proactive in seeking treatment tend to use CPAP more consistently [32].
While aspects such as depression and anxiety do not appear to have a major impact on adherence, claustrophobia may be a relevant factor. Patients with higher claustrophobic tendencies are more likely to struggle with adherence, suggesting that targeted interventions addressing these fears may be beneficial [33].

Social Support Factors

Social support plays a crucial role in enhancing adherence to CPAP therapy, with several studies highlighting its positive effects. For instance, research by Lewis et al. [34] demonstrated that individuals living with partners showed higher CPAP usage compared to those who lived alone.
Furthermore, Baron et al. [35] indicated that patients with high disease severity who perceived support from their spouses regarding CPAP treatment were more likely to adhere to therapy.
The quality of the couple's relationship and the partner's engagement in the treatment process play a crucial role in CPAP adherence too. Research by Gentina et al. [36] revealed that partner's encouragement of CPAP usage and a stable relationship exceeding 30 years were independent factors predicting CPAP adherence. Additionally, the study demonstrated that partner's engagement directly impacted CPAP adherence and improved symptoms, while CPAP adherence itself mediated disease-specific health-related quality of life. Importantly, marital quality acted as a moderator, with partner's engagement improving adherence only when the quality of marriage was high.

Clinical and Physiological Factors

The severity of OSAS, commonly assessed via AHI, has not consistently emerged as a reliable predictor. Similarly, the relationship between REM sleep-related OSA and adherence to CPAP therapy remains inconclusive, with mixed findings reported in the literature [27]. However, there is stronger evidence suggesting that the initial severity of daytime sleepiness can influence CPAP usage. Specifically, an ESS score greater than 10 has been identified as an independent predictor of long-term CPAP adherence [37]. Moreover, patients who exhibit the highest levels of adherence to CPAP therapy often report significant improvements in OSA-related symptoms, such as increased daytime energy levels and greater satisfaction with the treatment. This observed improvement in symptoms appears to correlate positively with continued CPAP usage, suggesting a potential bidirectional relationship between symptom relief and treatment adherence [38]. Composite indices of baseline sleep apnea severity have also been investigated and they better predict objective CPAP adherence and subjective treatment outcomes than baseline AHI and baseline ESS [39].

Technological factors

Despite the common assumption that side effects would negatively impact adherence, evidence suggests that they do not significantly affect patient compliance [40].

Mask-related problems such as improper fit, skin irritation, dry mouth, and nasal congestion can deter effective use. Although the type of PAP mask used at the start of treatment does not seem to significantly impact adherence, a variety of interfaces are now available [40].
Heated humidification was designed to alleviate dryness, but current evidence does not consistently demonstrate that this feature enhances adherence [41]. While heated humidification may alleviate symptoms like dry nasal passages and throat discomfort, its implementation should be tailored to individual needs.

Age-Related Factors

The influence of age on CPAP adherence presents a biphasic pattern. Research by Prigent et al. [42] reveals that adherence generally increases with age until 80 years, with a peak around 75-80 years. However, after 80 years, there is a significant decline in adherence rates, indicating a potential shift in factors influencing compliance. The study also found no correlation between adherence and gender, leaks, or residual AHI in individuals over 80 years, suggesting that factors beyond these traditional predictors may be at play in the elderly population.

Seasonal Factors

Seasonal changes can significantly impact CPAP adherence, particularly concerning ambient temperature. Recent research by Prigent et al. [43] demonstrated a notable decrease in PAP adherence during June compared to January, coinciding with warmer temperatures. This decline in adherence was observed across various mask types, age groups, and genders, suggesting a strong correlation with ambient temperatures. These findings have significant implications for healthcare providers, emphasizing the importance of addressing seasonal factors in patient education and support.

Telemonitoring Data-Based Predictors

Recent studies have begun to leverage telemonitoring data to investigate predictors of adherence to CPAP therapy, focusing on several parameters, including CPAP usage variability, leak rates, residual AHI, and device usage events.

- **CPAP Usage Variability:** A study by Eguchi et al. [44] analyzed data from telemonitoring systems: CPAP logs of 219 patients with OSAS were used. It was found that standard deviation of daily usage duration in a week possibly correlates to poor CPAP adherence. It means participants whose CPAP usage duration varies greatly in a week may have poor CPAP adherence; however, the sample size is insufficient to permit definitive conclusions to be drawn.

A further study [45] comprising 195 patients indicates that, although there was a moderate correlation between gender, the early patterns of CPAP use and long-term adherence, suggesting that early usage patterns may have some predictive value, there were instances where individuals with low initial usage later became long-term users. This indicates the need for a longer trial in some cases to make a definitive decision regarding long-term CPAP use. It suggests that a one-month trial of CPAP might be too short for some individuals.

- **Leak Rates and Residual AHI:** A pilot study [44] revealed that average daily air leakage in a week and average daily residual AHI in a week is possibly correlated to poor CPAP adherence because participants who experienced larger air leakage from a CPAP mask and higher residual AHI may have poor CPAP adherence. Additionally, another study revealed that patients exhibiting elevated levels of air leakage, adjusted for the delivered pressure, were more likely to be non-adherent to autoPAP therapy [46].

In summary, telemonitoring data presents a framework for identifying predictors of CPAP adherence by analyzing CPAP usage variability, leak rates, residual AHI, and device usage event.

Current literature underscores the multifaceted nature of predictors influencing CPAP adherence. Given the complexities of these factors, future research should focus on developing tailored interventions that target these predictors, promoting better adherence and improving overall health outcomes for patients with OSAS.

1.6 Objective

The goal of this thesis arises from addressing a **clinical problem** identified by pulmonologists: the overwhelming number of alerts concerning patients using devices [29], making it unfeasible to monitor each one effectively.
This research aims to characterize a new variable to divide patients into subgroups, enabling healthcare providers to focus on those with a high probability of non-adherence or poor treatment quality. While the literature has identified numerous factors associated with predicting good or poor adherence, no decisive element currently exists in daily practice to predict good adherence to CPAP.
The hypothesis posits that the psycho-behavioral aspect is the primary determinant of adherence to CPAP. This study will explore this aspect by analyzing how patients use CPAP, specifically investigating the variability in CPAP usage. This variability can be quantified by calculating the **monthly variance of adherence time series** obtained from telemonitoring data. This analysis seeks to determine whether CPAP usage patterns provide a meaningful indication of adherence and, ultimately, patient outcomes.

This exploration into the psycho-behavioral realm of CPAP adherence represents a novel approach to addressing the significant challenge faced by pulmonologists. By defining a new variable based on individual adherence patterns, the aim is to improve the ability of clinicians to predict and manage automatic device alerts, thereby enhancing patient outcomes and optimizing healthcare resource use.
The psycho-behavioral aspect can be quantified more comprehensively and accurately through a detailed characterization of the adherence time series, which may involve extracting numerous features (as demonstrated by the use of the time series feature extraction library in previous studies [47]). However, the limitation of this approach lies in its clinical applicability, as the goal is to provide physicians with a simple, intuitive, and practical method that can be applied without the need of complex algorithms.
The study will therefore quantify the predictive potential of monthly variance, its correlation with outcomes, and its capacity to categorize patients into subgroups.

1.6.1 Research Questions

1. Does monthly adherence variance correlate with short-, mid-, and long-term adherence and treatment quality?

2. Can monthly adherence variance categorize patients into three distinct subgroups with differing short-, mid-, and long-term adherence and treatment quality?

3. Are the patient clusters/subgroups identified using thresholds applied to monthly adherence variance stable over time?

Chapter 2

Methodology

2.1 Dataset description

The dataset used in this study is composed of telemonitoring data collected from patients with OSAS who were prescribed CPAP therapy in France. The data was provided by Elia Medical, a French company specializing in telemonitoring for respiratory diseases. The e-QUALISAS study analyzed one-month de-identified telemonitoring PAP-adherence data from a unique home-care provider (ELIA Medical) database in January, June and December 2021, including PAP adherence, device-reported residual AHI (AHIPAP) and 95th percentile non-intentional leaks. All adults were above the age of 18 years and started PAP before September 2020 and were treated for at least 4 months before the beginning of the study. All data were collected using the PAP-software (Airsense 10, Resmed, Australia). For each patient, monthly PAP adherence, AHI residual and 95th percentile non-intentional leaks means were calculated. PAP use (hours/night) was considered as the use during the 24 hours. Age and sex were also available in the database. All included adults gave their informed consent for data collection and anonymization. The study had been registered on Health Data Hub platform (N° F20220715144543). The dataset consists of two main parts:

- **Cohorte_données hebdo & mensuelles_Version du 30082022_pour Elia Medical.xlsx:** This file contains monthly and weekly data for 36,265 patients (rows), covering a period of three months (January, June, and December 2021). These data have been previously processed from raw data (described below). It includes the following variables (columns):
  - **SUBJID:** patient identifier;
  - **Nb Mois télésuivis:** number of telemonitoring months for the patient;
  - **Mois:** month of data (January, June, December);

  - **Num_mois:** month number (1: January, 2: June, or 3: December);
  - **Age:** patient age;
  - **Classe d'âge:** age category (categorized in 5-year intervals);
  - **Classe d'âge (pas = 10ans):** age category (categorized in 10-year intervals);
  - **Sexe:** patient gender ("Homme": Male, "Femme": Female);
  - **Agences:** name of the company associated with the patient;
  - **Code postal:** patient ZIP code;
  - **Région:** region in France;
  - **Ville:** city of the company;
  - **Zone allergie:** allergy area;
  - **Nom_marque_machine:** brand of CPAP device;
  - **Nom_machine:** supplier of CPAP device;
  - **Modèle machine:** model of CPAP device;
  - **Nom_masque:** model of CPAP mask;
  - **Type_masque:** type of CPAP mask (nasal, full-face);
  - **Nom_marque_masque:** mask supplier;
  - **Observance mensuelle moy:** monthly average CPAP adherence time (in hours);
  - **IAH mensuel moy:** monthly average AHI;
  - **Log10 IAH mensuel moy:** logarithm of monthly average AHI;
  - **Fuites 95e perc mensuelle moy (L/min):** monthly average leak rate at the 95th percentile;
  - **Log10 Fuites 95e perc:** logarithm of monthly average leak rate at the 95th percentile;
  - **Temps Fuites élevées mensuelle moy (min):** time when the leak rate was high;

- **Requete_Extraction_2021_01.xlsx**, **Requete_Extraction_2021_06.xlsx**, **Requete_Extraction_2021_12.xlsx:** These files contain daily data (rows) extracted from the telemonitoring system for each patient for each month (January, June, and December 2021, respectively). Due to the large volume of data (1154726, 1125852 and 1170822 lines, respectively), each file was split into two sheets to accommodate all the entries. These files represent the raw data used in the study as they are not previously processed, and the variables (columns) included in these files are:

- **nom_agence:** company name;
- **id_patient:** patient identifier;
- **id_materiel:** material identifier;
- **id_masque:** mask identifier;
- **date_releve:** date of data capture;
- **iah (AHI):** apnea-hypopnea index;
- **fuites:** leak rate at the 95th percentile;
- **utilisation_h:** CPAP usage time (in hours);
- **age:** patient age;
- **sexe:** patient gender.

The processed monthly and weekly data document is a subset of the raw data document, comprising a smaller set of patients. Consequently, the raw data document is the primary source for this study, the following section examines how it was preprocessed.

2.2 Data preprocessing

This section details the steps taken to preprocess the raw telemonitoring data into a format suitable for analysis. The preprocessing involved several stages, focusing on data cleaning, transformation, and structuring.

Loading raw data

The raw data was initially loaded from three Excel files: `Requete_Extraction_2021_01.xlsx`, `Requete_Extraction_2021_06.xlsx`, and `Requete_Extraction_2021_12.xlsx`. These files represent daily data for January, June, and December 2021, respectively. Each Excel file contained two sheets ("Result 1" and "Result 2") representing different portions of the same dataset.
The data was then loaded into three tables: `Gennaio` (January), `Giugno` (June), and `Dicembre` (December) which had different dimensions (1154726, 1125852 and 1170822 rows, respectively). This difference in number of rows reflects the fact that there are not the same number of daily acquisitions for all three months. To account for this variability and ensure a consistent dataset for analysis, a series of inclusion criteria were applied to the data (see Section 2.2.2).

Codification of strings into numbers

The `agency_name` and `sex` variables, which were initially categorical strings, were transformed into numerical values using a defined mapping.
For `agency_name`, each unique company name was assigned a unique numerical code, as shown in Table 2.1.

Agency Name	Code
'AIR ACTION SANTE'	1
'AUXILAIR NORD'	2
'AUXILAIR PICARDIE'	3
'ECVL'	4
'ELIA AQUITAINE'	5
'ELIA ATLANTIC'	6
'ELIA BFC'	7
'ELIA LCA'	8
'ELIA MEDICAL EST'	9
'ELIA MEDICAL OUEST'	10
'ELIA MEDICAL PARIS SAVIGNY'	11
'ELIA MEDITERRANEE - LUNEL'	12
'ELIA MEDITERRANEE - SEPTEMES LES VALLONS'	13
'ELIA NORD - PAS DE CALAIS'	14
'ELIA NORMANDIE'	15
'ELIA PACA'	16
'ELIA PICARDIE'	17
'ELIA RHONE ALPES'	18
'ELIA SUD OUEST'	19
'EMCA'	20
'EMPE'	21
'EMPO'	22
'UNIVAIR BMP'	23
'UNIVAIR GRAND EST'	24
'UNIVAIR MEDICAL CERGY'	25

Table 2.1: Mapping of agency names to numerical codes.

For `sex`, the Table 2.2 was applied. A review of the data revealed the existence of patients for whom a 'Mèdical' gender had been indicated, a designation that only carries meaningless information. In the following sections the removal of these patients from the study population will be highlighted (see Section 2.2.2).
The date variable was transformed to keep only the day of the month (dd-mm-yyyy). This transformation allows for a more efficient representation of categorical data,

Sex	Code
'Homme'	0
'Femme'	1
'Autre'	2
'Mèdical'	3

Table 2.2: Mapping of sex values to numerical codes.

facilitating subsequent data analysis through matrices.

From tables to matrices

The three matrices were created to store the data in a format more suitable for analysis in MATLAB. The size of these matrices remained the same as the original tables, but they only contained numerical values (`double`).

From matrices to structure

The three matrices were transformed into three structures (one for each month): `Gennaio_struct`, `Giugno_struct`, and `Dicembre_struct`. Each structure had a substructure for each patient, containing vectors (as long as the length of the month of the structure in days) for all variables:

- `agency_name`: vector containing company names associated with the patient;
- `material_ID`: vector containing material IDs for the patient;
- `mask_ID`: vector containing mask IDs for the patient;
- `date`: vector containing dates of data capture for the patient;
- `AHI`: vector containing AHI values for the patient;
- `leaks`: vector containing leak rates for the patient;
- `daily_adherence`: vector containing daily CPAP usage time for the patient;
- `age`: vector containing age values for the patient;
- `sex`: vector containing sex values for the patient.

The data from all three months structures was consolidated into a single structure, `database_struct` which had a substructure for each patient, containing:

- `agency_name`: single value;
- `material_ID`: single value;
- `mask_ID`: single value;

- `AHI`: structure containing three AHI vectors for each month;
- `leaks`: structure containing three leaks vectors for each month;
- `daily_adherence`: structure containing three daily CPAP usage time vectors for each month;
- `age`: single value;
- `sex`: single value.

The final consolidated structure, `database_struct`, is visualized in Figure 2.1. This structure contains substructures for each patient, such as `database_struct.patient_142` which is shown as illustrative example in Figure 2.2. Expanding the substructure for patient 142, we can see the field `Daily_adherence` (Figure 2.3). This field is itself a structure containing three fields representing the daily adherence vectors for each month: `gennaio` (January), `giugno` (June), and `dicembre` (December).

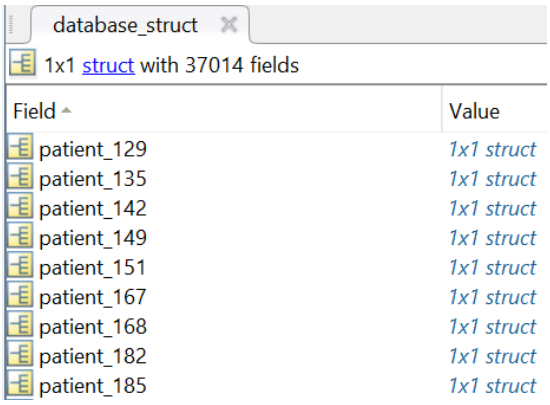


Figure 2.1: Visualization of the structure `database_struct`.

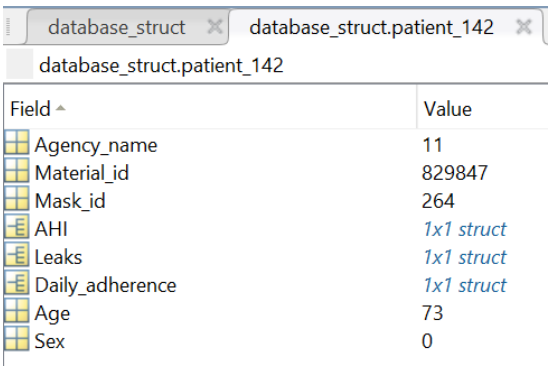


Figure 2.2: Visualization of the substructure `database_struct.patient_142`.

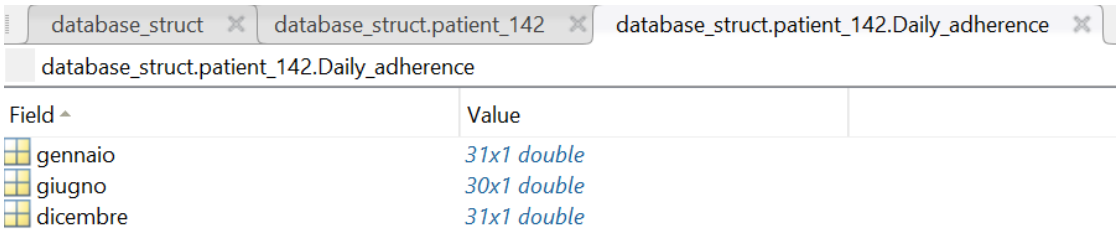


Figure 2.3: Visualization of the sub-sub-structure `database_struct.patient_142.Daily_adherence`.

2.2.1 Analysis and management of daily residual AHI and leaks values

This section addresses the analysis and handling of daily residual AHI and leak rate values. Following discussions with clinicians, particular attention was paid to these values due to the observation of anomalous patterns atuomatically measured from the device. The presence of inconsistencies – such as residual AHI or leaks recorded during periods of zero CPAP usage – necessitates careful management. Our approach ensures that these inconsistencies are appropriately identified and treated. The following subsections describe the specific steps taken to process these values, including handling of missing data, detection of outliers, and imputation strategies.

Inconsistent values

In the preprocessing stage, each daily value of residual AHI and leaks corresponding to zero CPAP daily usage was replaced with an empty value (NaN) to eliminate inconsistencies in the data. Prior to this correction, these values were set to 0, which introduced inconsistency. Specifically, the double null value both in adhesion and residual AHI (or leaks) implies that achieving zero adhesion would result in the optimal values for residual AHI (or leaks) as to achieve optimality, these variables must be minimised. From this point onwards, all calculations (in particular the extraction of monthly features) are conducted without considering the empty values. In addition, a new feature is introduced which quantifies the number of empty values (days of non-use of CPAP) per month. Adopting this approach allows the additional feature to provide a direct measure of the non-use of the device. However, this approach doesn't solve the potential bias that could arise from the monthly average of residual AHI and leaks, which does not take into account empty values. An alternative approach could have involved using a weighted average, where a quantity proportional to the number of monthly missing values would be added to the average calculated without considering the missing values. However, such a correction can be complex and requires a careful evaluation of the parameters involved (in this case, the weight to be assigned to the monthly number of missing values). This approach was not selected since a suitable method for accurately determining the parameter in question had not been identified. Additional potential methods include imputation and interpolation. However, these were excluded because by definition when the device is not utilised, no measurements are produced; a solution to the problem would have been achieved at a more straightforward data processing stage, however, this approach would have resulted in inconsistencies with the daily adherence feature. Given these considerations, the solution ultimately adopted involves capturing the number of non-use days as a distinct metric, while excluding these days from the calculations

of monthly mean residual AHI and leaks.

Outlier values in literature

The reliability of residual AHI calculation by PAP devices has been the subject of investigation in more than one study [48, 49, 50]. These studies compare the AHI determined by the CPAP machine with the AHI determined by manual reading of a polysomnography (AHI_PSG) during the same night. The findings demonstrate that (i) software machines tend to overestimate the AHI when the AHI_PSG is low and the AHI is underestimated when the AHI_PSG is high, (ii) the correlation between the machine index and the AHI_PSG is found to be acceptable for apneas, but markedly inferior for hypopnoeas, (iii) the precision of residual AHI calculation by the device is reduced when higher pressure is applied to the patient.

Outlier detection

In light of the observations made, an investigation was conducted into the outliers present in the device daily measurements of residual AHI and leaks. The data from the consolidated structure (`database_struct`) was transformed into a single daily matrix: the rows of the matrix represented the daily acquisition for each month for each patient while the columns showed the features: patient_id, month of data capture (1: January, 6: June, 12: December), day of the month, daily CPAP usage time (in hours), daily AHI, daily leak rate. This transformation facilitated the analysis of daily AHI and leaks values in relation to daily adherence.

The optimal approach for the identification of outliers would have been to use the Mahalanobis distance, incorporating the information about the pressure delivered by the device. This would have been advantageous due to the established relationship between the accuracy of the measurements and the delivered pressure, as mentioned earlier. However, since the pressure data were unavailable, an alternative outlier detection method based on a histogram analysis of the general trend of the residual AHI and leaks variables was employed [51]. This approach is a univariate, non-parametric statistical method, which relies on the distribution of the data without making a priori assumptions about their trend, allowing for a more flexible identification of outliers.
A threshold is defined and an outlier is defined as a daily measurement that exceeds the threshold.

Outlier imputation

The imputation strategy was based on clustering the data according to daily adherence values, which can take on a finite number of values, specifically ranging from 0h to 24h in increments of 0.1h. Each measurement belonging to the same level of daily adherence was considered a single cluster, and outliers were imputed within these clusters. The outlier values were imputed by replacing each outlier within the cluster with the median of the remaining non-outlier values calculated within the same cluster.

2.2.2 Inclusion criteria

These inclusion criteria were established to ensure the completeness and consistency of the dataset, allowing for reliable analysis across all patients over the three months. The criteria related to valid mask ID, gender, age, and daily adherence were implemented to eliminate erroneous or incomplete data, improving the accuracy of the results.
Furthermore, the criteria were refined through consultations with clinicians. More detailed explanations regarding the rationale behind each specific criterion are provided in section 3.2.
Patients were included in the analysis if they met the following criteria:

1. Complete data across all three months: the patient must have data for all three months.

2. Complete data for the month: the number of data points in the `daily_adherence` vector must equal the number of days in the month: 30 acquisitions for January, 31 for June and 30 for December.

3. Valid mask ID: the `mask_id` value must not be null.

4. Valid gender: the `sex` value must not be "Medical", indicating a data error.

5. Valid age: the `age` value must not be empty.

6. Daily adherence less than 24 hours: the `daily_adherence` values should not exceed 24 hours.

7. Specific device: the `nom_machine` must be "S10 Resmed".

8. Minimum monthly adherence: the monthly mean of `daily_adherence` must be greater than or equal to 2 hours.

To conclude the data preprocessing and move towards feature extraction, the final dataset has been consolidated into a structure named `database_struct_8criteri`, which includes the patients who met the established inclusion criteria and for which outlier imputation of daily values has been performed.

2.3 Feature extraction

In this paragraph, we describe the process of extracting features from the dataset in order to prepare it for further analysis. This procedure uses the preprocessed dataset, specifically `database_struct_8criteri`, where imputation and inclusion criteria have already been applied. At the end of this step a matrix named `database_matr_8criteri` is obtained: for each patient (row) 38 columns are obtained. For each patient, key data such as agency name, material ID, age, and sex (Electronic Health Record features) are extracted, followed by the computation of various statistical and binary features related to adherence, leaks, and AHI.

EHR features

Each patient in the dataset is identified by a unique patient ID, which is extracted by converting the patient's alphanumeric string identifier into a numeric form. This allows for efficient management of the data within the matrix. Additionally, the basic information for each patient (: `agency_name`, `material_ID`, `age`, and `sex`) is captured in the first five columns of the matrix.

Statistical features

For each patient, the variance in CPAP adherence (VarAdh) is computed for the months of January, June, and December. This metric helps assess the fluctuation in the number of hours of device usage on a day-to-day basis during these months. Variance values are stored in the next three columns (6-8 columns) of the matrix.

The mean adherence (MeanAdh) in hours, 95th percentile leaks in L/min (MeanLeaks), and AHI (MeanAhi) for each month (January, June, and December) are calculated as the monthly averages, ignoring any `NaN` values where applicable. These mean values provide a summary of the patient's usage, leakage, and AHI performance over time. The computed averages are stored in the columns 9-17.

Monthly labels

In addition to the numerical features, we compute a series of binary labels that provide a classification of each patient's adherence, leak rate, and AHI values based on certain thresholds which were defined in close collaboration with pulmonologists.

Binary variables are calculated based on whether the monthly mean adherence exceeds 4 hours per night (columns 18-20: Adh4) or 5 hours per night (columns 21-23: Adh5). These two thresholds were considered based on their clinical and regulatory significance. The first threshold of 4 hours was selected because, as explained in Section 1.5, the National French guidelines for CPAP reimbursement stipulate that patients must use the device for more than 4 hours per night to qualify for full reimbursement [26]. Although there is no consensus regarding the optimal level of PAP usage relative to health outcomes, a threshold of daily adherence of more than 4 h is commonly considered as an adequate level of treatment [52]. The second threshold of 5 hours was introduced with the aim of identifying high-quality treatment adherence. It serves as one of the three criteria (the other two are the next two explained) combined to define whether a patient is receiving optimal therapy which is correlated to blood pressure, symptoms, depression, road traffic accidents, cardiovascular morbidity and mortality, all-cause hospitalization and emergency visits, all-cause mortality, health costs [52] as shows figure 2.4.

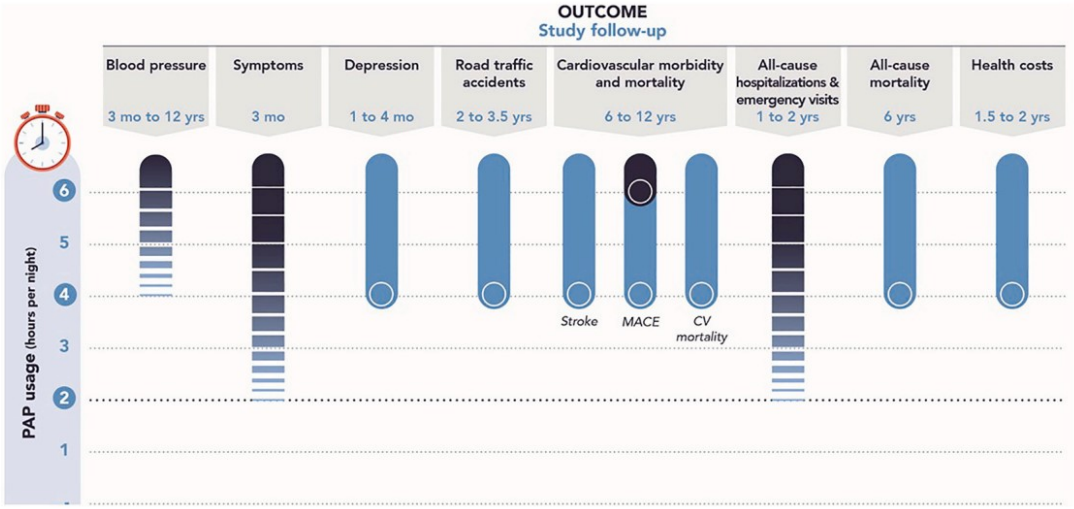


Figure 2.4: Association between PAP usage and outcomes based on published literature. Non-solid bars show studies in which PAP usage was analyzed as a continuous variable. Plain bars show studies that evaluated the impact of PAP usage above and below a predefined threshold [52].

The next set of binary indicators (columns 24-26: Leaks24) is calculated based on whether the average leak rate for each month is less than 24 L/min. This threshold is set based on the analysis by Schwab et al. [53], which considers this value of leak rate at the 95th percentile for a ResMed device as acceptable. According to the analysis, a leak rate below this threshold allows scheduling a follow-up clinical

appointment between 6 months and one year, as it indicates that the patient's therapy is within the acceptable performance range.

Similarly, binary labels for AHI are computed based on whether the monthly mean AHI is below 5 events per hour (columns 27-29: Ahi5) always defined from Schwab et al. [53] a value considered to lead to an effective treatment.

Lastly, we calculate combined criteria (columns 30-33: CC), which combine adherence, leak, and AHI metrics to assess patient performance under stricter conditions. If all the three criteria are positive this metric is positive which means the patient reached a good quality treatment.

Numerical features

The last three columns (33-35: NullAdh) in this subsection count the number of `NaN` values in the AHI measurements for each month. These values indicate the number of days in each month where CPAP usage was zero by directly quantifying the number of days when the CPAP device was not used. The decision to include this variable in the analysis is explained in Section 2.2.1, where it was determined that capturing the number of non-use days as a distinct metric provides complementary information to the monthly statistical variables.

2.4 Calculation of the correlation coefficients

In this section, the correlation coefficients are computed to examine the relationships between various EHR features, VarAdh and outcomes metrics across three different months (January, June, and December). Specifically, the correlation is calculated between the following independent variables: agency name, material ID, age, sex, and VarAdh for each month (JA: January, JU: June, DE: December), and the dependent variables (along the rows) for each month (JA, JU, DE), which include MeanAdh, MeanLeaks, MeanAhi, Adh4, Adh5, Leaks24, Ahi5, CC, and NullAdh.

The correlation is calculated using the Pearson method when the dependent variable is continuous (MeanAdh, MeanLeaks, MeanAhi, NullAdh), and the Kendall method when the dependent variable is binary (Adh4, Adh5, Leaks24, Ahi5, CC). Specifically, the Pearson or Kendall correlation coefficient r can range from -1 to 1. A value of $r = 1$ indicates a perfect positive correlation, $r = -1$ represents a perfect negative correlation, and $r = 0$ signifies no correlation. For practical purposes, the following ranges are used to classify the strength of the correlation:

- Weak correlation: $|r|$ between 0 and 0.3

- Moderate correlation: $|r|$ between 0.3 and 0.7
- Strong correlation: $|r|$ greater than 0.7

These thresholds provide a framework for evaluating the correlation coefficients calculated in this analysis.

The principal objective of this calculation was to quantify and compare the correlation between the novel variable VarAdh and the outcomes under examination, and the correlation between the variables that had already been analysed in a previous study [42] based on the same database and the outcomes. This preliminary analysis was conducted to provide an early indication of whether the initial hypothesis regarding the predictive potential of the VarAdh variable could indeed lead to the desired results in subsequent analyses.

In addition to calculating the correlation coefficients, the p-value associated with each correlation was computed to assess the statistical significance of the results. The p-value determines whether the observed correlation could have occurred by chance, with a lower p-value indicating a more statistically significant relationship. For this analysis, a threshold of $p < 0.05$ was used to denote statistical significance. The p-values were calculated for both the Pearson correlation (for continuous variables such as MeanAdh, MeanLeaks, MeanAhi, and NullAdh) and the Kendall correlation (for binary variables such as Adh4, Adh5, Leaks24, Ahi5, and CC).

2.5 Univariate clustering

Univariate clustering is an unsupervised method which involves defining clusters within the population of the dataset based solely on a single variable, which in this case is the VarAdhJA variable. This approach was employed to assess the ability of VarAdhJA to separate patients into distinct clusters with differing characteristics and to stratify them, particularly with regard to their long-term outcomes. By focusing on this single variable, the goal was to understand its effectiveness in differentiating patient groups and its potential in predicting future clinical results. This method allows us to explore how a single key feature like VarAdhJA can influence patient stratification and contribute to meaningful distinctions in treatment response or adherence patterns.

2.5.1 Hierical clustering

Initially, hierarchical clustering was employed because this type of clustering does not require the number of clusters to be defined a priori. This method allows for

an exploratory analysis, enabling the data structure to guide the determination of appropriate clusters. Based on the analysis of the dendrogram generated by the hierarchical clustering, a specific number of clusters to investigate was chosen. The flexibility of this method provided a good foundation for the initial exploration of the dataset.

Hierarchical agglomerative clustering is a method that builds a hierarchy of clusters by iteratively merging the closest pairs of clusters. The process begins with each data point as its own cluster, and in each step, the two clusters that are closest to each other are merged. This continues until all data points are grouped into a single cluster. The hierarchical structure is typically visualized using a **dendrogram**, which shows how clusters are merged over the process, with the height of the branches representing the distance between the merged clusters.
Clusters can be extracted from the dendrogram by making a "cut" at a certain height, which divides the dendrogram into distinct clusters. There are two main ways to perform this cutting:

- Natural Cutting: This method relies on identifying a natural gap in the dendrogram where the distances between clusters increase significantly. By visually inspecting the dendrogram, one can determine a level where the structure of the data suggests a clear division of clusters. This natural gap often represents the most meaningful division according to the inherent properties of the data.
- Highest Distance Cutting: In this approach, the dendrogram is cut at the highest possible distance between clusters. This ensures that the clusters formed are maximally distinct from one another based on the distance metric used. It is particularly useful when the goal is to maximize the separation between groups.

By applying hierarchical agglomerative clustering, flexibility is provided in selecting the most appropriate number of clusters based on the data structure and the analysis goals.The distance metric used in this clustering process was the Euclidean distance, which measures the straight-line distance between points in the dataset. The linkage criterion was based on the complete method, where the distance between clusters is determined by the maximum distance between any pair of points in the clusters being merged.

2.5.2 K-means

Following the utilisation of the dendrogram for the visualisation of the data, the decision was taken to apply the K-means clustering method with a pre-defined

number of clusters (k). This was based on insights gained from the dendrogram analysis and discussions with clinicians.

The K-means algorithm is a simple clustering method that seeks to minimize the intra-cluster variability and maximize the inter-cluster distance in an iterative process. The centroid, or prototype, represents the mean value of all the elements that belong to a given cluster. Intra-cluster variability refers to the sum of all distances between each element within a cluster and the centroid of that cluster. On the other hand, inter-cluster distance is the distance between the centroids of two different clusters. The algorithm was applied using the MATLAB function `kmeans`. The function was executed with default settings, meaning that the algorithm performed the clustering with the default number of 100 maximum iterations per run and 5 repetitions (or restarts), this means the algorithm will run 5 times with different initial centroid positions and return the solution with the lowest total sum of distances within clusters.

The K-means algorithm operates in several steps. First, the number of clusters k is defined. Then, k initial centroids are selected, either by assigning elements arbitrarily to clusters or by choosing an arbitrary set of cluster centroids, with some elements acting as centroids. Once the centroids are set, the algorithm computes the centroid of each cluster. After this, it reassigns each element in the dataset to the nearest centroid based on a predefined distance measure. This process of recalculating centroids and reassigning elements continues iteratively until the assignment of all elements no longer changes. If no change occurs, the algorithm stops; otherwise, it repeats the process until convergence is achieved.

2.5.3 Single-threshold clustering

An additional method was explored to partition the dataset into only two clusters using a single threshold. The optimal threshold was identified through the evaluation of a ROC curve (Receiver Operating Characteristic curve). The ROC was constructed by varying the threshold on the continuous variable VarAdhJA, which dichotomises the dataset based on the binary variable Adh4DE. This means that the ROC curve was calculated to identify the optimal threshold on the adherence variance in January that could best classify patients in December as either adherent or non-adherent (defined as having a monthly usage of more than 4 hours per night).
Following the construction of the ROC curve, the threshold value applied to the VarAdhJA variable was selected to maximise Youden's Index.

ROC Curve

A ROC curve is a graphical representation used to evaluate the performance of a binary classification model at different threshold settings. It plots the True Positive Rate (sensitivity) against the False Positive Rate (1 - specificity) for various threshold values. The area under the ROC curve (AUC) provides a measure of the model's ability to distinguish between classes, with a value of 1 representing perfect classification and 0.5 representing a model that performs no better than random guessing. The ROC curve is particularly useful in determining the optimal balance between sensitivity and specificity by visualizing the trade-off between these two metrics at different threshold levels.

Youden's Index

Youden's Index is a summary measure used to determine the optimal threshold for a classification model based on its ROC curve. It is calculated as:

$$\text{Youden's Index} = \text{Sensitivity} + \text{Specificity} - 1$$

The index ranges from 0 to 1, with higher values indicating better performance. The optimal threshold is the one that maximizes Youden's Index, meaning it provides the best balance between sensitivity (true positive rate) and specificity (true negative rate).
Geometrically, Youden's Index represents the vertical distance between a point on the ROC curve and the diagonal line (also called the line of no-discrimination), which represents random guessing. The diagonal corresponds to a scenario where the classifier has no discriminative ability (i.e., a random classifier).This makes it a useful metric for selecting the threshold that maximizes the model's ability to correctly classify both positive and negative cases.

2.6 Clusters characterization

Once the clusters were identified, they were characterized to understand the specific properties and features of each group. Each cluster was characterized by:

- numerosity: number of patients within that cluster;
- % population: percentage of patients in that cluster relative to the entire dataset population;
- Age: mean value and standard deviation of the age of patients within that cluster;

- Sex: percentages of 'Male', 'Female', and 'Others' patients separately in that cluster;
- VarAdh: mean value and standard deviation of the monthly variance of adherence for each month for each cluster;
- MeanAdh: mean value and standard deviation of the monthly mean adherence for each month for each cluster;
- MeanLeaks: mean value and standard deviation of the monthly mean unintentional leaks at the 95th percentile for each month for each cluster;
- MeanAhi: mean value and standard deviation of the monthly mean AHI for each month for each cluster;
- Adh4: percentages of patients meeting the adherence criterion (MeanAdh>4) for each month for each cluster;
- Adh5: percentages of patients meeting the adherence criterion for good quality treatment (MeanAdh>5) for each month for each cluster;
- Leaks24: percentages of patients meeting the leak criterion for good quality treatment (MeanLeaks<24) for each month for each cluster;
- Ahi5: percentages of patients meeting the AHI criterion for good quality treatment (MeanAhi<10) for each month for each cluster;
- CC: percentages of patients meeting the combined criterion (MeanAdh>5 & MeanLeaks<24 & MeanAhi<10) for each month for each cluster;
- NullAdh: mean value and standard deviation of the number of nights per month with no device usage for each month for each cluster.

For each variable, the p-value was also calculated:

- For the numerical variables (Age, VarAdh, MeanAdh, MeanLeaks, MeanAhi, NullAdh), the p-value was computed using a one-way ANOVA test. This test returns a p-value, which quantifies the statistical difference between at least one cluster and the others for that specific variable. Additionally, from one-way ANOVA test a structure is returned that is used in the multiple comparison test, enabling us to determine which pairs of group means are significantly different from each other.
- For the binary or categorical variables (Sex, Adh4, Adh5, Leaks24, Ahi5, CC), the p-value was computed using a chi-squared test. First, a contingency table

was created, followed by the chi-squared statistic calculation. The degrees of freedom and the cumulative distribution function were then used to obtain the p-value.

The p-values are reported for each variable only when greater than 0,001, otherwise, '< 0,001' is reported. The p-values are highlighted in **bold** when statistically significant (less than 5%). Additionally, for each variable, next to the value of each cluster, symbols are included to indicate which clusters share statistically significant inter-cluster differences.
In addition to the general characterization of clusters, a specific analysis was conducted on the distribution of the variable MeanAdhDE within and across the identified clusters. This was performed by visualizing three overlapping histograms, one for each cluster, with a bar width of 0,1h. The x-axis represents the values of the MeanAdhDE variable (mean adherence in December), while the y-axis indicates the occurrences (i.e., the number of patients) within that interval for each cluster.

2.6.1 Longitudinal analysis

An additional analysis was conducted on the clusters obtained through the single-threshold method, focusing on a longitudinal temporal perspective. This analysis aimed to quantify adherence outcomes and treatment quality based on how many months (out of the three examined: January, June, and December) a patient remained in the cluster characterized by lower adherence variance. Essentially, it evaluates the outcomes as a function of membership in this cluster over time.

This was achieved by subdividing the clusters generated by applying the ROC-determined threshold to the variable VarAdhJA (January adherence variance) into sub-clusters. These sub-clusters were created by applying the same threshold to the variable VarAdhJU (June adherence variance). Subsequently, further subdivision into "sub-sub-clusters" was performed by applying the threshold to the variable VarAdhDE (December adherence variance).

The "sub-sub-clusters" were then merged into four distinct clusters:

1. Patients who did not belong to the lower-variance cluster in any of the three months.

2. Patients who belonged to the lower-variance cluster for one month.

3. Patients who belonged to the lower-variance cluster for two months.

4. Patients who belonged to the lower-variance cluster for all three months.

For each of these four clusters, these outcomes were characterized: MenAdhDE (mean adherence in December), percentage of patients meeting the adherence criterion (%Adh4DE), and percentage of patients achieving optimal treatment quality (%CCDE). The results were visualized using bar plots, with error bars representing the standard deviation and statistical significance indicated by asterisks placed above the bars when significant differences were found. The overall statistical difference was quantified through the calculation of p-values (considered significant when $< 5\%$). Specifically, one-way ANOVA was used to test for differences in the continuous variable MeanAdhDE, while chi-squared tests were employed to assess the differences in the binary variables Adh4DE and CCDE. This approach follows the methodology outlined in Section 2.6.

This longitudinal analysis provided valuable insights into how sustained membership in the low-variance cluster influences adherence and treatment quality outcomes over time.

Chapter 3

Results

In this chapter, the key findings from the analysis of telemonitoring data collected from patients undergoing CPAP therapy are presented. The results chapter is structured to address various aspects of the study, beginning with the identification and treatment of outliers in daily measurements of AHI and leaks, followed by the implementation of inclusion criteria to refine the dataset. The performance of the proposed feature, Variance in Adherence (VarAdh), is evaluated, with correlations and clustering techniques applied to assess its potential in predicting long-term treatment outcomes. Finally, a detailed characterization of the patient clusters is provided, offering insights into the relationship between adherence

3.1 Analysis and management of daily residual AHI and leaks values

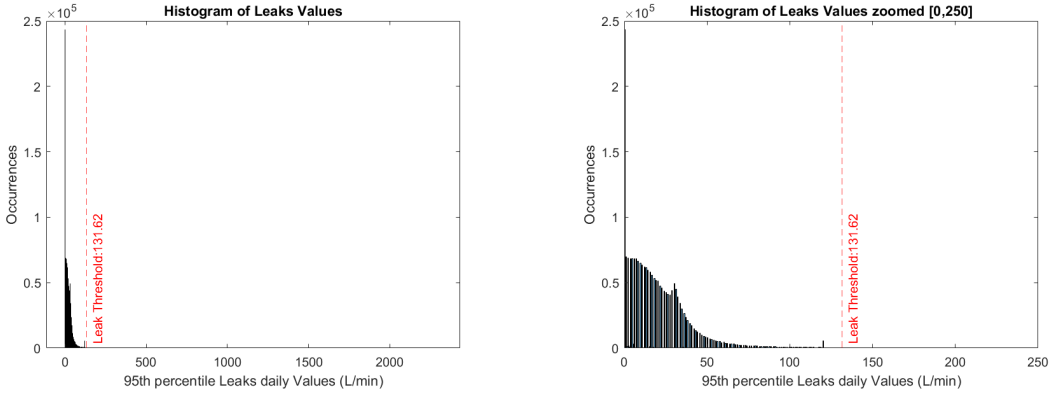
3.1.1 Inconsistent values

The correction applied to residual AHI and leaks values resulted in 275.172 data points being marked as NaN out of 2.414.908 total values from patients who met up to the seventh exclusion criterion (as outlined in Section 2.2.2), removing any inconsistencies arising from periods of zero CPAP usage. This adjustment allowed for a more accurate calculation of monthly averages, as empty values were excluded from the analysis, ensuring that residual AHI and leak rates were not artificially minimized.

Furthermore, the new feature quantifying the number of non-use days per month will have its significance explained in the following sections.

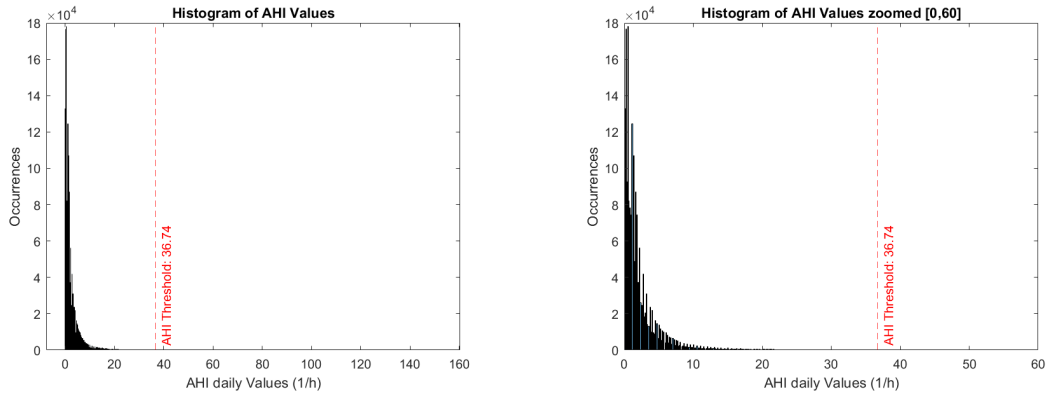
3.1.2 Outlier detection

Thresholds were set as the average value plus nine times the standard deviation of the distribution of residual AHI for AHI outlier detection and the average value plus six times the standard deviation of the distribution of leaks for daily measurements of leaks outlier detection in order to set a quite conservative threshold. Figures 3.1 A, 3.2 A and figures 3.1 B, 3.2 B demonstrate the conservative nature of the thresholds and show that only a small tail of the total distribution is actually considered as outliers.



A) B)

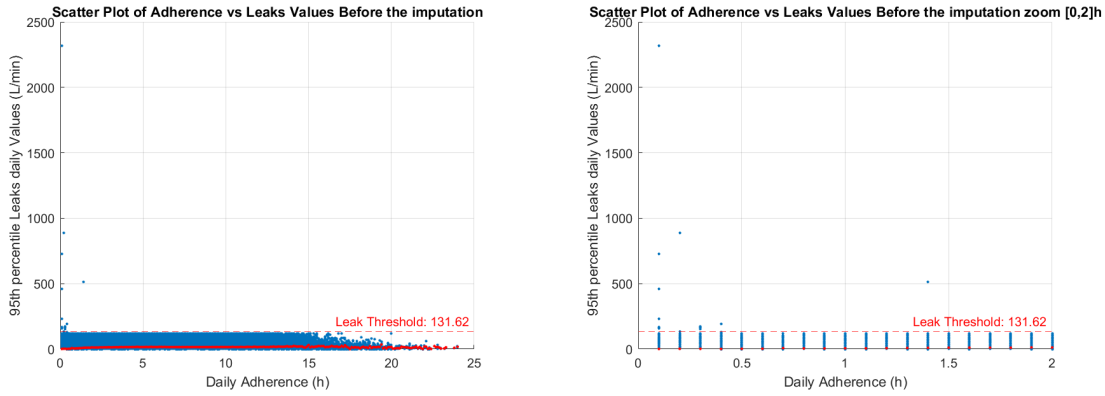
Figure 3.1: A) Histogram of daily non-intentional leaks. B) Zoomed histogram of daily non-intentional leaks between 0 and 250 (L/min).



A) B)

Figure 3.2: A) Histogram of daily AHI. B) Zoomed histogram of daily AHI between 0 and 60 (1/h).

Figures 3.3 A and 3.4 A depict a scatter plot illustrating the daily leaks measurements and daily AHI measurement as a function of the hours of use of the CPAP with the superimposed thresholds. The figures 3.3 B and 3.4 B depict a zoomed scatter plot in the adherence range between 0 and 2 hours.
In figures 3.3 and 3.3, A) representation of data is given because a greater presence of outliers was noted when the hours of daily use were low. The purpose of representation B) is twofold: firstly, to illustrate the trend of measurements in very low daily adherence levels more precisely; secondly, to demonstrate the discrete levels of adherence measured (rounding to the first decimal place in the calculation of daily adherence). This observation will be employed at a later stage during the imputation process (Sections 2.2.1 and 3.1.3).



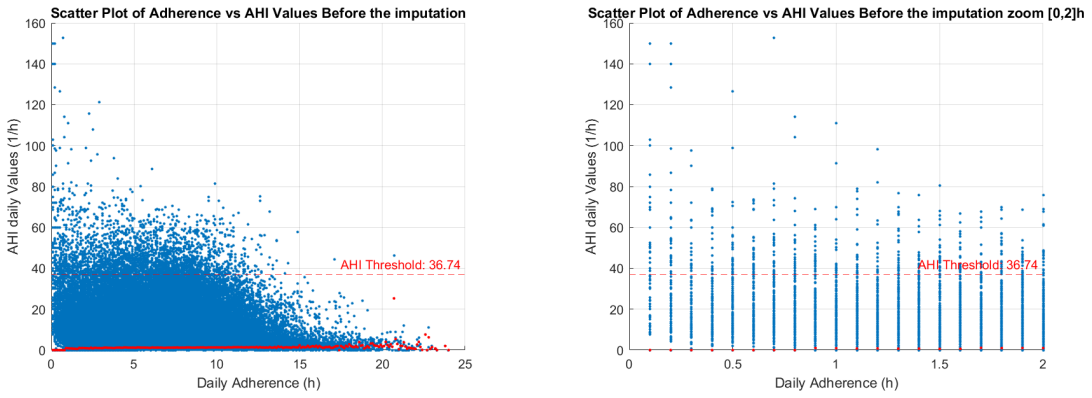
A) B)

Figure 3.3: A) Scatter plot of daily leaks measurements as a function of hours of CPAP use. B) Zoomed scatter plot of daily leaks measurements in the adherence range between 0 and 2 hours.

3.1.3 Outlier imputation

Following the identification of outliers in the daily residual AHI and leaks values, which were classified as erroneous based on a review of the literature and consultations with clinicians, an imputation strategy was implemented. Outliers were imputed within each adherence cluster, based on the median values of the remaining non-outlier measurements as explained in Section 2.2.1. This approach aimed to preserve the integrity of the dataset by replacing extreme values that could skew the overall results.

Finally, 3.164 and 119 daily AHI values and daily leaks values, respectively, where imputed out of 2.414.908 daily measurements.



A) B)

Figure 3.4: A) Scatter plot of daily AHI measurements as a function of hours of CPAP use. B) Zoomed scatter plot of daily AHI measurements in the adherence range between 0 and 2 hours.

3.2 Inclusion criteria

The figure 2.1 illustrates, in a flowchart, how the database was reduced from 37.790 patients to 24.253 patients.

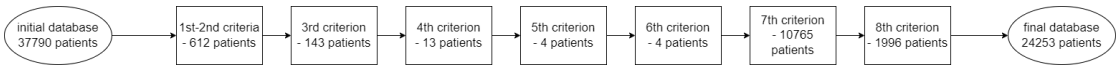


Figure 3.5: Flowchart showing the steps of the reduction of the database from 37.790 patients to 24.253 patients through the eight criteria enumerated in Section 2.2.2.

The first two criteria (Complete data across all three months and Complete data for the month) were established to ensure a comprehensive dataset. The subsequent criteria (Valid mask ID, Valid gender, Valid age, and Daily adherence less than 24 hours) were implemented to eliminate missing or inconsistent values.
The seventh criterion addresses the variability in the definitions of leaks among different manufacturers, as discussed in Section 1.5.1. Consequently, we decided to focus our investigation on the model and device most prevalent in the dataset, which is the Resmed S10.
The eighth criterion was adopted following the feature extraction phase. The minimum monthly adherence criterion was implemented because, after consultation with clinicians, patients who do not meet this standard are considered to be less representative of the target population for this study. This is primarily due to the fact that they may not qualify for government reimbursement [26], which can

create significant barriers to ongoing treatment. Additionally, without sufficient adherence to CPAP usage, these patients are less likely to experience meaningful improvements in their condition [28, 52].

3.3 Correlation coefficients

The correlation coefficients between the independent variables (AgencyName, MaterialID, Age, Sex, and VarAdh) and the dependent variables (MeanAdh, MeanLeaks, MeanAhi, Adh4, Adh5, Leaks24, Ahi10, CC, and NullAdh) were calculated, as described in Section 2.4. These calculations were performed on two datasets: one containing patients with MeanAdhJA lower than 2 hours per night (7-criteria database, Table 3.6) and another excluding these patients (8-criteria database, Table 3.7). The aim was to quantify the relationships between the newly introduced variable, VarAdh, and key dependent variables to assess its predictive potential compared to already investigated independent variables, and to evaluate the impact of applying 8 criteria instead of 7.
The correlation was measured across three different months (JA, JU, and DE). In the tables (3.6 and 3.7), each cell represents the correlation coefficient calculated between the independent variable (in the columns) and the dependent variable (in the rows). The color of the cell indicates the time span of the correlation: yellow for short-term (same month), blue for medium-term (six months), and green for long-term (twelve months). Statistical significance is denoted by the boldness of the coefficient, with bold indicating a p-value less than 0.05 (p-values were calculated for all correlation coefficients and are reported in tables 3.8 and 3.9). The color of the coefficient itself reflects the strength of the correlation: black for weak, orange for moderate, and red for strong correlations.

The quantitative comparison clearly shows that VarAdh offers a much stronger and consistent correlation with key dependent variables related to adherence and treatment quality.
There is a difference in correlation when the dataset is reduced further to include only patients with MeanAdhJA greater than two hours per night (the 8-criteria dataset). In the table representing the correlations calculated on the reduced dataset, the coefficients are significantly higher. By excluding these patients, we observe a much stronger linear relationship between the independent and dependent variables, particularly for VarAdh, whose correlation coefficients increase markedly, as seen in the comparison between the two tables.

In table 3.7, the long-term correlations (green cells) offer a detailed comparison

Correlation table from database_matr_7criteri			Indipendent variables						
			AgencyName	**MaterialID**	**Age**	**Sex**	**VarAdh**		
							JA	JU	DE
Dipendent variables	**MeanAdh**	JA	**-0,04**	0,00	**0,12**	**-0,05**	**-0,21**		
		JU	**-0,04**	0,00	**0,11**	**-0,03**	**-0,20**	**-0,21**	
		DE	**-0,04**	-0,01	**0,10**	**-0,05**	**-0,19**	**-0,17**	**-0,17**
	MeanLeaks	JA	0,00	**0,02**	**0,22**	**-0,07**	**0,04**		
		JU	-0,01	**0,02**	**0,22**	**-0,07**	**0,02**	**0,04**	
		DE	0,01	**0,03**	**0,22**	**-0,06**	**0,02**	**0,02**	**0,03**
	MeanAhi	JA	0,01	**0,02**	**0,21**	**-0,11**	0,01		
		JU	**0,02**	**0,02**	**0,20**	**-0,11**	0,00	**0,02**	
		DE	0,01	**0,01**	**0,21**	**-0,10**	0,01	**0,01**	**0,02**
	Adh4	JA	**-0,03**	-0,01	**0,08**	**-0,04**	**-0,06**		
		JU	**-0,03**	0,00	**0,07**	**-0,04**	**-0,11**	**-0,09**	
		DE	**-0,03**	**-0,01**	**0,06**	**-0,05**	**-0,10**	**-0,07**	**-0,03**
	Adh5	JA	**-0,02**	0,00	**0,07**	**-0,06**	**-0,18**		
		JU	**-0,02**	0,00	**0,06**	**-0,04**	**-0,19**	**-0,20**	
		DE	**-0,02**	-0,01	**0,06**	**-0,05**	**-0,17**	**-0,15**	**-0,15**
	Leaks24	JA	-0,01	-0,01	**-0,15**	**0,05**	**0,05**		
		JU	0,00	-0,01	**-0,16**	**0,06**	**0,03**	**0,05**	
		DE	**-0,02**	**-0,02**	**-0,16**	**0,04**	**0,02**	**0,03**	**0,06**
	Ahi5	JA	**-0,02**	**-0,02**	**-0,10**	**0,07**	**0,11**		
		JU	**-0,03**	**-0,02**	**-0,10**	**0,06**	**0,06**	**0,12**	
		DE	**-0,02**	**-0,01**	**-0,10**	**0,06**	**0,04**	**0,06**	**0,13**
	CC	JA	**-0,01**	**-0,01**	**-0,11**	**0,03**	**-0,10**		
		JU	**-0,01**	**-0,02**	**-0,11**	**0,04**	**-0,10**	**-0,12**	
		DE	**-0,03**	**-0,02**	**-0,13**	**0,03**	**-0,05**	**-0,04**	**-0,02**
	NullAdh	JA	**0,05**	0,00	**-0,13**	**0,05**	**0,22**		
		JU	**0,04**	0,00	**-0,11**	**0,03**	**0,20**	**0,21**	
		DE	**0,04**	0,01	**-0,10**	**0,06**	**0,20**	**0,16**	**0,18**

Figure 3.6: Correlation table calculated on the 7-criteria database.

Correlation table from database_matr_8criteri			Indipendent variables						
			AgencyName	**MaterialID**	**Age**	**Sex**	**VarAdh**		
							JA	JU	DE
Dipendent variables	**MeanAdh**	JA	-0,01	**0,02**	**0,08**	**-0,03**	-0,42		
		JU	**-0,01**	0,01	**0,06**	**-0,02**	-0,34	-0,35	
		DE	**-0,01**	0,00	**0,05**	**-0,05**	-0,32	**-0,27**	**-0,29**
	MeanLeaks	JA	0,01	**0,02**	**0,22**	**-0,07**	**0,04**		
		JU	0,00	**0,02**	**0,22**	**-0,07**	**0,03**	**0,04**	
		DE	**0,01**	**0,03**	**0,22**	**-0,07**	**0,02**	**0,02**	**0,03**
	MeanAhi	JA	**0,01**	**0,03**	**0,22**	**-0,11**	0,01		
		JU	**0,02**	**0,02**	**0,21**	**-0,11**	0,01	**0,02**	
		DE	0,01	**0,01**	**0,22**	**-0,11**	0,01	**0,02**	**0,02**
	Adh4	JA	**-0,01**	0,01	**0,04**	**-0,03**	**-0,23**		
		JU	**-0,02**	0,00	**0,03**	**-0,03**	**-0,25**	**-0,20**	
		DE	**-0,02**	-0,01	**0,02**	**-0,05**	**-0,23**	**-0,18**	**-0,14**
	Adh5	JA	-0,01	0,01	**0,04**	**-0,05**	-0,31		
		JU	-0,01	0,00	**0,03**	**-0,03**	-0,30	-0,30	
		DE	-0,01	-0,01	**0,03**	**-0,05**	**-0,28**	**-0,24**	**-0,24**
	Leaks24	JA	-0,01	-0,01	**-0,18**	**0,06**	-0,01		
		JU	0,00	-0,01	**-0,18**	**0,06**	**-0,01**	0,00	
		DE	**-0,02**	**-0,02**	**-0,17**	**0,05**	**-0,01**	-0,01	**0,01**
	Ahi5	JA	-0,01	**-0,01**	**-0,15**	**0,09**	0,00		
		JU	**-0,02**	**-0,02**	**-0,14**	**0,08**	-0,01	**0,02**	
		DE	-0,01	**-0,01**	**-0,14**	**0,07**	**-0,02**	0,00	**0,05**
	CC	JA	0,00	**-0,01**	**-0,14**	**0,04**	**-0,16**		
		JU	0,00	**-0,02**	**-0,14**	**0,05**	**-0,15**	**-0,16**	
		DE	**-0,02**	**-0,02**	**-0,16**	**0,04**	**-0,10**	**-0,08**	**-0,07**
	NullAdh	JA	**0,02**	**-0,01**	**-0,10**	**0,05**	**0,75**		
		JU	**0,01**	0,00	**-0,05**	**0,04**	0,44	0,45	
		DE	**0,02**	0,01	**-0,05**	**0,06**	0,39	0,32	0,37

Figure 3.7: Correlation table calculated on the 8-criteria database.

between VarAdhJA, Sex, and Age as independent variables, and key dependent variables such as MeanAdh, Adh4, CC, and NullAdh. Focusing on the long-term

P-values related to correlation table from database_matr_7criteri			Indipendent variables						
			AgencyName	**MaterialID**	**Age**	**Sex**	**VarAdh**		
							JA	JU	DE
Dipendent variables	**MeanAdh**	JA	0,00	0,96	0,00	0,00	0,00		
		JU	0,00	0,75	0,00	0,00	0,00	0,00	
		DE	0,00	0,29	0,00	0,00	0,00	0,00	0,00
	MeanLeaks	JA	0,84	0,01	0,00	0,00	0,00		
		JU	0,35	0,00	0,00	0,00	0,00	0,00	
		DE	0,09	0,00	0,00	0,00	0,01	0,00	0,00
	MeanAhi	JA	0,06	0,00	0,00	0,00	0,11		
		JU	0,00	0,00	0,00	0,00	0,49	0,00	
		DE	0,21	0,03	0,00	0,00	0,15	0,04	0,00
	Adh4	JA	0,00	0,27	0,00	0,00	0,00		
		JU	0,00	0,63	0,00	0,00	0,00	0,00	
		DE	0,00	0,03	0,00	0,00	0,00	0,00	0,00
	Adh5	JA	0,00	0,69	0,00	0,00	0,00		
		JU	0,00	0,96	0,00	0,00	0,00	0,00	
		DE	0,00	0,05	0,00	0,00	0,00	0,00	0,00
	Leaks24	JA	0,02	0,19	0,00	0,00	0,00		
		JU	0,36	0,06	0,00	0,00	0,00	0,00	
		DE	0,00	0,00	0,00	0,00	0,00	0,00	0,00
	Ahi5	JA	0,00	0,00	0,00	0,00	0,00		
		JU	0,00	0,00	0,00	0,00	0,00	0,00	
		DE	0,00	0,00	0,00	0,00	0,00	0,00	0,00
	CC	JA	0,02	0,00	0,00	0,00	0,00		
		JU	0,01	0,00	0,00	0,00	0,00	0,00	
		DE	0,00	0,00	0,00	0,00	0,00	0,00	0,00
	NullAdh	JA	0,00	0,45	0,00	0,00	0,00		
		JU	0,00	0,53	0,00	0,00	0,00	0,00	
		DE	0,00	0,10	0,00	0,00	0,00	0,00	0,00

Figure 3.8: P-value table relating to correlation coefficients calculated on the 7-criteria database.

P-values related to correlation table from database_matr_8criteri			Indipendent variables						
			AgencyName	**MaterialID**	**Age**	**Sex**	**VarAdh**		
							JA	JU	DE
Dipendent variables	**MeanAdh**	JA	0,43	0,01	0,00	0,00	0,00		
		JU	0,03	0,41	0,00	0,00	0,00	0,00	
		DE	0,02	0,94	0,00	0,00	0,00	0,00	0,00
	MeanLeaks	JA	0,38	0,00	0,00	0,00	0,00		
		JU	0,74	0,00	0,00	0,00	0,00	0,00	
		DE	0,03	0,00	0,00	0,00	0,00	0,00	0,00
	MeanAhi	JA	0,04	0,00	0,00	0,00	0,13		
		JU	0,00	0,00	0,00	0,00	0,26	0,00	
		DE	0,13	0,04	0,00	0,00	0,07	0,02	0,00
	Adh4	JA	0,03	0,33	0,00	0,00	0,00		
		JU	0,01	0,78	0,00	0,00	0,00	0,00	
		DE	0,01	0,15	0,00	0,00	0,00	0,00	0,00
	Adh5	JA	0,28	0,25	0,00	0,00	0,00		
		JU	0,26	0,41	0,00	0,00	0,00	0,00	
		DE	0,35	0,28	0,00	0,00	0,00	0,00	0,00
	Leaks24	JA	0,23	0,23	0,00	0,00	0,12		
		JU	0,95	0,06	0,00	0,00	0,04	0,84	
		DE	0,00	0,00	0,00	0,00	0,01	0,20	0,01
	Ahi5	JA	0,17	0,01	0,00	0,00	0,68		
		JU	0,00	0,00	0,00	0,00	0,09	0,00	
		DE	0,24	0,02	0,00	0,00	0,00	0,84	0,00
	CC	JA	0,66	0,03	0,00	0,00	0,00		
		JU	0,39	0,00	0,00	0,00	0,00	0,00	
		DE	0,00	0,00	0,00	0,00	0,00	0,00	0,00
	NullAdh	JA	0,00	0,05	0,00	0,00	0,00		
		JU	0,03	0,83	0,00	0,00	0,00	0,00	
		DE	0,01	0,29	0,00	0,00	0,00	0,00	0,00

Figure 3.9: P-value table relating to correlation coefficients calculated on the 8-criteria database.

predictions, we can observe that VarAdhJA consistently demonstrates stronger correlations across these variables compared to Sex and Age.
Starting with MeanAdh, VarAdhJA shows a correlation of -0.32, which is significantly higher than both Sex (-0.05) and Age (0.05).
For Adh4, which represents the proportion of patients meeting the minimum monthly adherence threshold of 4 hours per day , VarAdhJA again shows a higher correlation -0.23 than either Sex (-0.05) or Age (0.02).
Looking at the combined criteria (CC), which evaluates adherence, leak rates, and AHI together, VarAdhJA demonstrates a weak long-term correlation of -0.10 higher than Sex but not than Age.
Lastly, in relation to long-term prediction of NullAdh, which quantifies the monthly number of days without CPAP usage, VarAdhJA shows a moderate correlation of 0.39. This is markedly higher than both Sex (0.06) and Age (-0.05).

The Pearson correlation coefficient between VarAdhJA and MeanAdhDE is -0.32, indicating a moderately negative correlation. The negative sign suggests that higher variability in adherence in January is associated with lower average adherence in December, meaning that patients with inconsistent adherence early on tend to have worse adherence outcomes at the end of the year.
The Pearson correlation coefficient between VarAdhJA and NullAdhDE is 0.39, indicating a moderate positive correlation. The positive sign suggests that greater variance in adherence in January strongly predicts an increase in the monthly number of days of non-use (NullAdh) in December.
Finally, the Kendall coefficient between VarAdhJA and CCDE is -0.10, which, although weaker, still indicates a negative correlation. The coefficient suggests that greater variance in adherence in January corresponds to a lower likelihood of achieving the combined criteria (CC) in December. While the correlation is not as strong as with MeanAdh, the negative sign confirms that higher adherence variability is linked to poorer overall treatment quality, as measured by CC.

3.4 Univariate clustering

3.4.1 Hierarchical clustering

In the initial phase of the hierarchical clustering analysis, a cut based on the highest distance was tested. The dendrogram obtained and the cut performed (at a distance of 48,41 h), which divides the patients into clusters colored with different colors, is shown below in figure 3.10.
Following the analysis based on the highest distance cut, a natural cut was tested, as the initial approach was found to be unsatisfactory and inadequate, at a distance of 8,6 h. This height was chosen because it allows for the division of the dataset

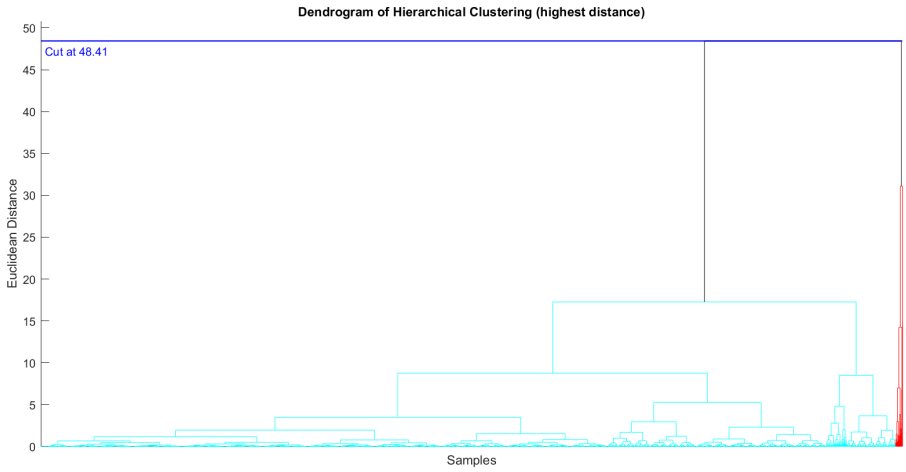


Figure 3.10: Dendrogram of Hierarchical Univariate Clustering cut at the highest distance (max_dist = 48,41) obtaining 2 clusters.

into a number of clusters that is not too high, yet still sufficiently stratifies the data.
The dendrogram obtained and the natural cut performed, which resulted in a division of the data into 8 clusters, is shown below in figure 3.11.

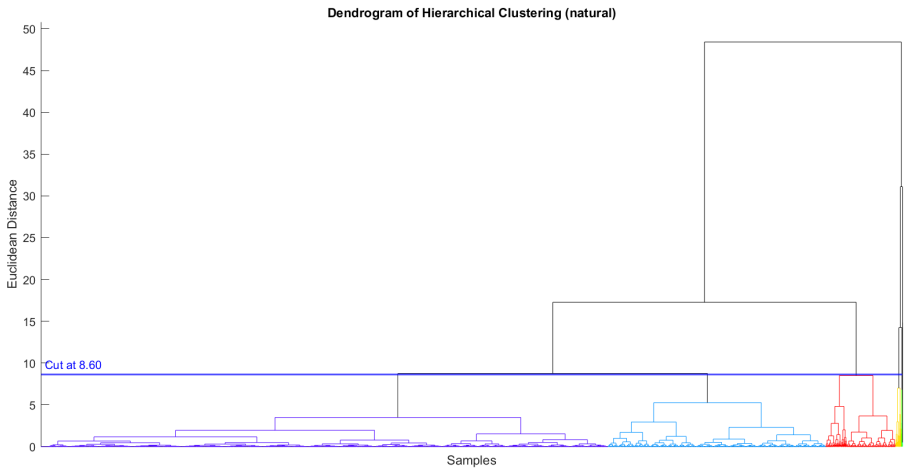


Figure 3.11: Dendrogram of Hierarchical Univariate Clustering cut through natural cut (dist = 8,6) obtaining 8 clusters.

This natural cut provided the best way to explore the inherent structure of the

data, allowing for the identification of the number of patient clusters that are likely to have meaningful differences in terms of outcomes or other characteristics.

3.4.2 K-means clustering

This approach allows for the number of clusters to be chosen a priori, offering greater control over the final grouping. Division into 3 clusters were investigated based on discussions with clinicians and supported by the results of the dendrogram analysis. The dendrogram graphic representation of data revealed a primary division of the population into three large groups, with additional smaller secondary groups. This evidence guided the selection of 3 clusters, striking a balance between capturing key distinctions within the larger clusters and ensuring that the number of groups remains manageable for practical application in clinical practice. This compromise helps maintain high efficiency while allowing for detailed patient stratification. The K-means algorithm was applied, and the function defined two thresholds to distinguish between three clusters: Th1 = 3,8004 and Th2 = 9,7338 hours of adherence variance in January.

The figure below (3.12) displays the results of the K-means clustering applied to the VarAdhJA variable, with the patients grouped into three clusters. The x-axis represents the variance in adherence during January (VarAdhJA), while the y-axis represents patient IDs. The scatter plot visualizes the separation between clusters, with each color corresponding to a distinct cluster: Cluster 1 in green with lowest variance, Cluster 2 in orange with medium variance and Cluster 3 with highest variance. This representation was chosen, despite the y-axis not conveying specific information, to visually display the density of elements within the clusters based solely on the VarAdhJA scale.

Figures 3.13 and 3.14 visualize the clustered data, in terms of MeanAdhJA vs VarAdhJa and MeanAdhDE vs VarAdhJa.

These visualizations help us understand the qualitative relationship between VarAdhJA and MeanJA/MeanDE across the clusters. In particular, they highlight how patients with higher variability in adherence tend to have lower mean adherence values.

However, this graphical representation primarily serves as a preliminary exploration of these relationships. The exact quantification of these differences between clusters, including additional variables, is provided in detail in the next section (Section **??**), where the properties of each cluster are further analyzed and compared.

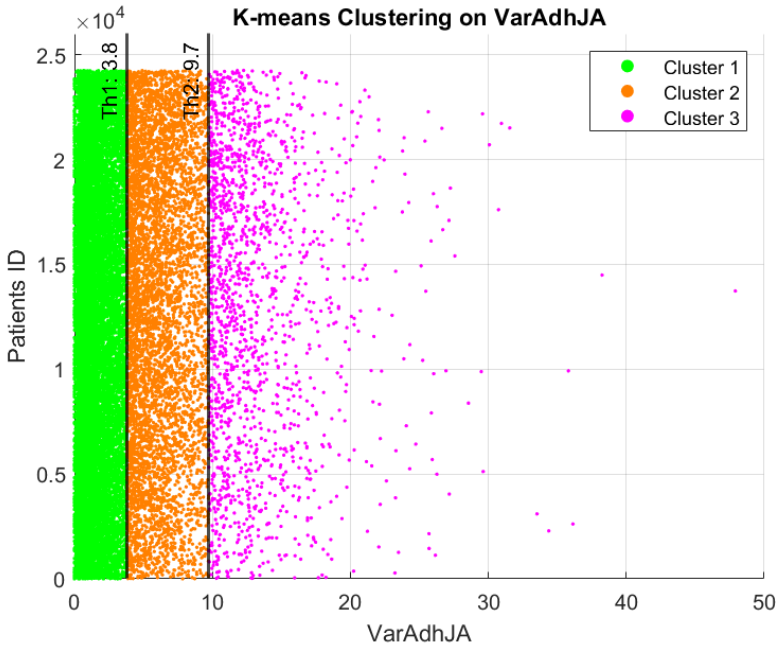


Figure 3.12: K-means clustering of patients based on VarAdhJA. Two thresholds (Th1=3,8h and Th2=9,7h) are shown, separating the three clusters.

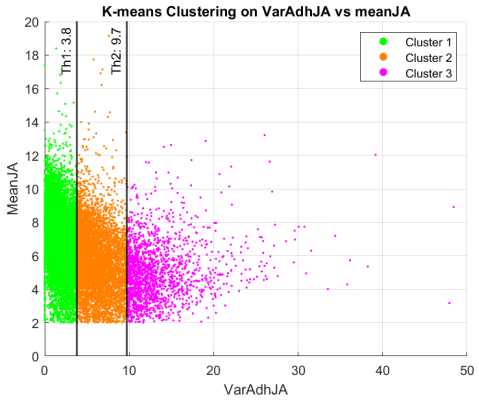


Figure 3.13: K-means clustering results: the x-axis represents the variance in adherence in January (VarAdhJA), while the y-axis represents the mean adherence in January (MeanJA).

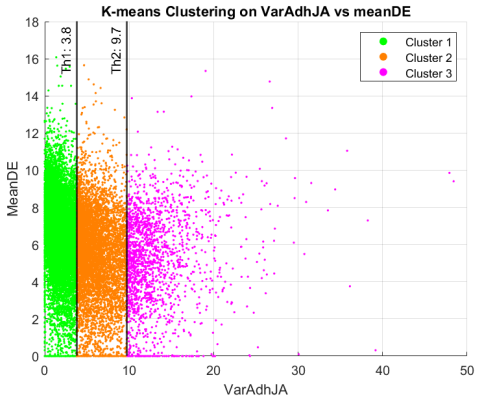


Figure 3.14: K-means clustering results: the x-axis represents the variance in adherence in January (VarAdhJA), while the y-axis represents the mean adherence in December (MeanDE).

3.4.3 Single-threshold clustering

As outlined in the Methods chapter (Section 2.5.3), a ROC curve was constructed by varying the threshold applied to the variable VarAdhJA and evaluating its effects on the binary variable Adh4DE (monthly adherence greater than 4 hours in December). The ROC curve allows us to assess the ability of the adherence variance in January (VarAdhJA) to predict whether a patient will meet the adherence criterion (Adh4DE) by December.

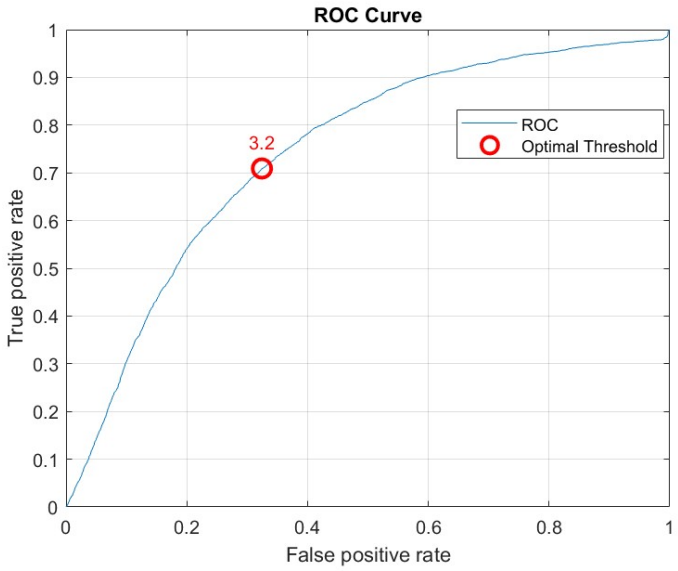


Figure 3.15: ROC curve obtained by varying the threshold applied to the variable VarAdhJA and evaluating its effects on the binary variable Adh4DE (AUC = 0,7417). The optimal threshold (= 3,1683 hours) with the maximum Youden's Index (= 0,4357) is highlighted in red.

Figure 3.15 presents the ROC curve obtained from this analysis. The AUC corresponding to this ROC is 0,7417, indicating a reasonably good ability of the VarAdhJA to predict future adherence outcomes. The optimal threshold, which maximizes Youden's Index, is marked with a red circle on the graph. The optimal threshold identified was 3,1683 hours of monthly adherence variance. This threshold yields a Youden's Index of 0,4357, representing the best balance between sensitivity and specificity for predicting adherence behavior in December based on January's variance in adherence.

The optimal threshold value of 3,2 hours, being very close to the Th1 threshold (3,8 hours as shown in Section 3.4.2) obtained during the K-means clustering for distinguishing between Cluster 1 and Cluster 2, reinforces the significance of

Cluster1.

Figures below (Figure 3.16,3.17 and 3.18) illustrate the results of the single-threshold clustering applied to the VarAdhJA variable, using the optimal threshold of 3,2 hours identified in the previous ROC analysis.

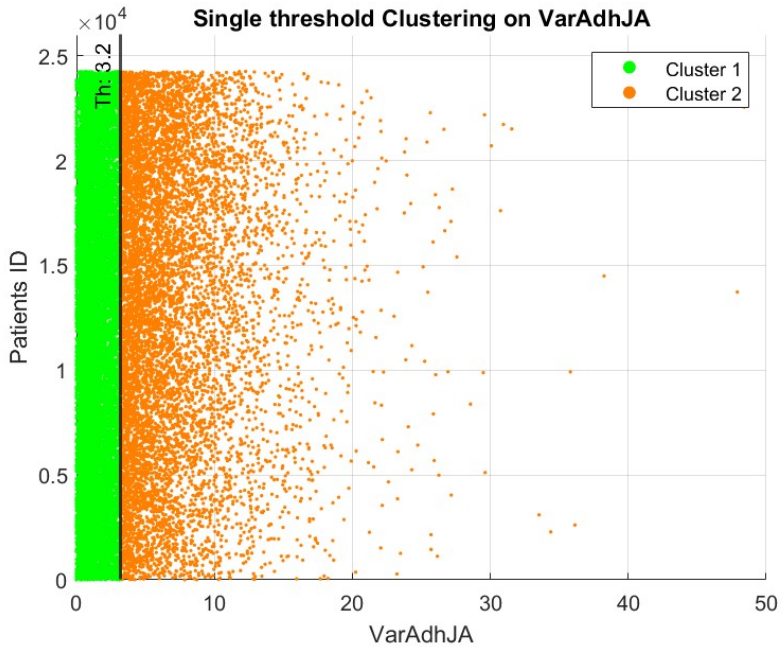


Figure 3.16: Single-threshold clustering of patients based on VarAdhJA with the threshold of 3,2h separating the two clusters: the x-axis represents the variance in adherence during January (VarAdhJA), while the y-axis represents patient IDs.

Following this analysis, the two clusters derived from the single-threshold approach will be characterized similarly to how the three clusters from the K-means clustering were characterized. This includes evaluating numerosity, adherence patterns, and other key metrics (detailed explanation in Section 2.6 and 3.5). Additionally, the relevance of remaining within Cluster 1, not only in January but also in June and December, will be assessed in terms of ensuring high-quality treatment and adherence over time. This longitudinal perspective will help to identify patients who consistently fall within Cluster 1 throughout the year.

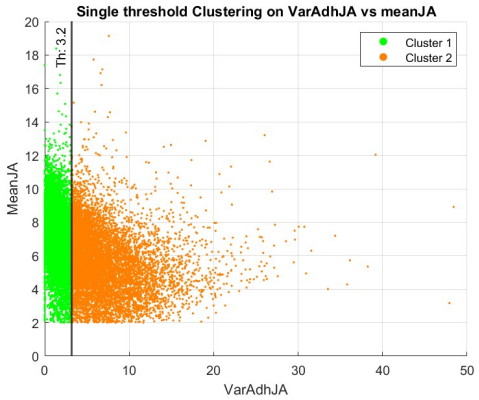


Figure 3.17: Single-threshold clustering results: the x-axis represents the variance in adherence during January (VarAdhJA), while the y-axis represents mean adherence in January.

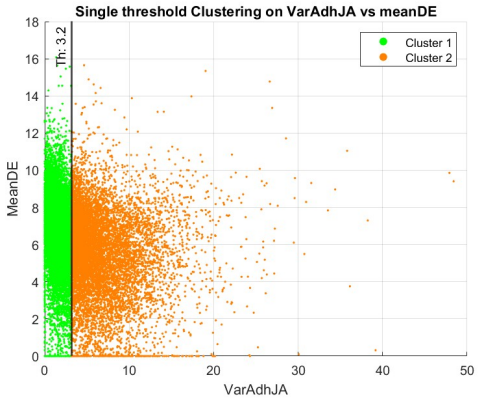


Figure 3.18: Single-threshold clustering results: the x-axis represents the variance in adherence during January (VarAdhJA), while the y-axis represents mean adherence in December.

3.5 Clusters characterization

3.5.1 K-means cluster characterization

The identified three K-means clusters were analyzed to compare the characteristics of each group. Table 3.19 provides a detailed summary of the variables for each cluster, including numerosity, age , adherence patterns, and key therapy-related metrics like AHI and leak rates.
To visualize the similarity between Cluster 2 and Cluster 3, Figure 3.21 shows the distribution of the variable MeanAdhDE across the different clusters obtained through K-means clustering.
From this graph, it is possible to qualitatively appreciate the extent to which Cluster 1 differs from the other clusters in terms of mean adherence values and standard deviation. This difference is more pronounced than that observed between Cluster 2 and Cluster 3, which is relatively slight.

3.5.2 Single-threshold cluster characterization

The same characterization applied to the clusters obtained using the k-means method has been performed on the clusters obtained with the single-threshold method. The difference in this case is that only two clusters were identified instead of three. Therefore, the use of multiple comparison tests is not necessary, and statistical inter-cluster differences are already indicated by the p-value reported in

Characterization of the clusters obtained through **kmeans** clustering applied to database_matr_8criteri		Cluster 1	Cluster 2	Cluster 3	p-value
numerosity		16609	5972	1672	
% population		68,5%	24,6%	6,9%	
Age		64.23 ± 12.25 (◊○□)	61.22 ± 13.20 (◊○□)	60.09 ± 14.31 (◊○□)	**< 0,001**
Sex	Male	70,3% (◊○)	64% (◊)	60,9% (○)	**< 0,001**
	Female	29,7% (◊○)	36% (◊)	39% (○)	
	Others	0% (◊○)	0% (◊)	0,1% (○)	
VarAdh	JA	1.53 ± 1.00 (◊○)	6.07 ± 1.63 (◊□)	13.40 ± 3.96 (○□)	**< 0,001**
	JU	2.07 ± 2.25 (◊○)	4.96 ± 3.12 (◊□)	7.78 ± 5.07 (○□)	**< 0,001**
	DE	2.41 ± 2.63 (◊○)	5.43 ± 3.62 (◊□)	8.41 ± 5.76 (○□)	**< 0,001**
MeanAdh	JA	7.21 ± 1.59 (◊○)	5.70 ± 1.86 (◊□)	5.03 ± 1.73 (○□)	**< 0,001**
	JU	6.69 ± 1.69 (◊○)	5.23 ± 2.11 (◊□)	4.96 ± 2.40 (○□)	**< 0,001**
	DE	6.91 ± 1.88 (◊○)	5.40 ± 2.31 (◊□)	5.20 ± 2.57 (○□)	**< 0,001**
MeanLeaks	JA	18.39 ± 15.03 (◊○)	19.07 ± 15.28 (◊□)	20.39 ± 16.20 (○□)	**< 0,001**
	JU	20.29 ± 15.95 (◊)	20.86 ± 16.40	21.68 ± 17.18 (◊)	**< 0,001**
	DE	19.19 ± 15.49 (◊)	19.39 ± 15.59	20.29 ± 16.64 (◊)	**0,03**
MeanAhi	JA	2.30 ± 2.80	2.34 ± 2.85	2.37 ± 2.81	0,5
	JU	2.26 ± 2.66	2.27 ± 2.72	2.30 ± 2.76	0,81
	DE	2.20 ± 2.67	2.25 ± 2.84	2.33 ± 2.94	0,1
Adh4	JA	96,3% (◊○)	81,7% (◊□)	70,8% (○□)	**< 0,001**
	JU	93,3% (◊○)	73,2% (◊□)	67,6% (○□)	**< 0,001**
	DE	93% (◊○)	74,6% (◊□)	69,7% (○□)	**< 0,001**
Adh5	JA	91,2% (◊○)	64,7% (◊□)	45,9% (○□)	**< 0,001**
	JU	85,7% (◊○)	55,8% (◊□)	51,6% (○□)	**< 0,001**
	DE	86,7% (◊○)	60,1% (◊□)	54,8% (○□)	**< 0,001**
Leaks24	JA	70,4% (○)	69,7% (□)	67,1% (○□)	**0,016**
	JU	65,3% (○)	63,9% (□)	61,3% (○□)	**0,002**
	DE	68,1% (○)	67,4% (□)	63,3% (○□)	**< 0,001**
Ahi5	JA	89,4%	89,1%	88,6%	0,458
	JU	89,3% (○)	88,5%	87,4% (○)	**0,039**
	DE	89,3% (◊○)	87,5% (◊□)	85% (○□)	**< 0,001**
CC	JA	58,6% (◊○)	41,2% (◊□)	27% (○□)	**< 0,001**
	JU	51,6% (◊○)	33,6% (◊□)	29,5% (○□)	**< 0,001**
	DE	59,1% (◊○)	47,5% (◊□)	42,9% (○□)	**< 0,001**
NullAdh	JA	0.20 ± 0.70 (◊○)	3.37 ± 3.67 (◊□)	9.21 ± 5.12 (○□)	**< 0,001**
	JU	0.89 ± 2.96 (◊○)	4.36 ± 6.23 (◊□)	7.87 ± 8.07 (○□)	**< 0,001**
	DE	1.17 ± 3.88 (◊○)	4.92 ± 7.16 (◊□)	8.13 ± 8.67 (○□)	**< 0,001**

Figure 3.19: Characterization of the clusters obtained through k-means clustering applied to `database_matr_8criteri`. The table shows the variables across the three clusters, along with the corresponding p-values for each variable. Significant p-values are highlighted in **bold**, and symbols indicate inter-cluster differences.

the last column of the table.
The table below (Table 3.20) provides a detailed summary of the variables for each of the two clusters, including numerosity, age, adherence patterns, and key therapy-related metrics such as AHI and leak rates. As with the k-means clustering results, p-values were calculated for each variable. The p-values in bold indicate statistically significant differences between the two clusters.

Characterization of the clusters obtained through **single-threshold** clustering applied to database_matr_8criteri		Cluster 1	Cluster 2	p-value
numerosity		15161	9092	
% population		62,5%	37,5%	
Age		64.41 ± 12.23	61.19 ± 13.29	**< 0,001**
Sex	Male	70,7%	63,8%	**< 0,001**
	Female	29,3%	36,2%	
VarAdh	JA	1.34 ± 0.83	7.01 ± 3.83	**< 0,001**
	JU	1.94 ± 2.15	5.25 ± 3.74	**< 0,001**
	DE	2.27 ± 2.56	5.73 ± 4.24	**< 0,001**
MeanAdh	JA	7.28 ± 1.56	5.69 ± 1.86	**< 0,001**
	JU	6.77 ± 1.65	5.28 ± 2.15	**< 0,001**
	DE	6.99 ± 1.83	5.47 ± 2.35	**< 0,001**
MeanLeaks	JA	18.35 ± 15.00	19.27 ± 15.47	**< 0,001**
	JU	20.27 ± 15.93	20.96 ± 16.50	**0,001**
	DE	19.22 ± 15.51	19.48 ± 15.74	0,212
MeanAhi	JA	2.30 ± 2.80	2.34 ± 2.84	0,358
	JU	2.25 ± 2.64	2.29 ± 2.74	0,328
	DE	2.20 ± 2.68	2.24 ± 2.81	0,268
Adh4	JA	96,8%	81,2%	**< 0,001**
	JU	94,1%	73,8%	**< 0,001**
	DE	93,9%	75,2%	**< 0,001**
Adh5	JA	92,2%	63,7%	**< 0,001**
	JU	87,2%	57,4%	**< 0,001**
	DE	88,1%	61,1%	**< 0,001**
Leaks24	JA	70,4%	69,3%	0,062
	JU	65,3%	63,7%	**0,011**
	DE	68,0%	66,8%	0,066
Ahi5	JA	89,5%	89,0%	0,271
	JU	89,3%	88,4%	**0,02**
	DE	89,3%	87,3%	**< 0,001**
CC	JA	59,3%	40,2%	**< 0,001**
	JU	52,4%	34,4%	**< 0,001**
	DE	59,5%	47,8%	**< 0,001**
NullAdh	JA	0.13 ± 0.52	4.06 ± 4.56	**< 0,001**
	JU	0.78 ± 2.79	4.64 ± 6.58	**< 0,001**
	DE	1.05 ± 3.71	5.12 ± 7.39	**< 0,001**

Figure 3.20: Characterization of the clusters obtained through single-threshold clustering applied to `database_matr_8criteri`. The table shows the variables across the two clusters, along with the corresponding p-values for each variable. Significant p-values are highlighted in **bold**.

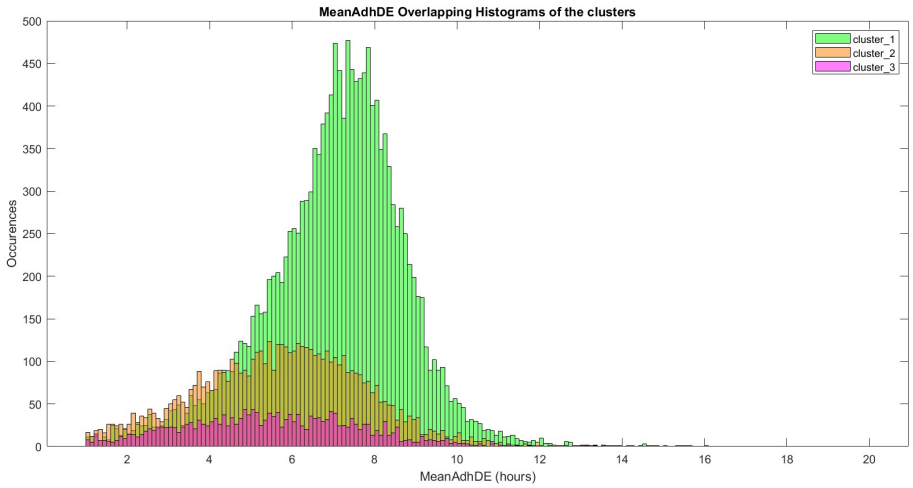


Figure 3.21: Overlapping histograms showing the distribution of MeanAdhDE across the three clusters obtained through K-means clustering.

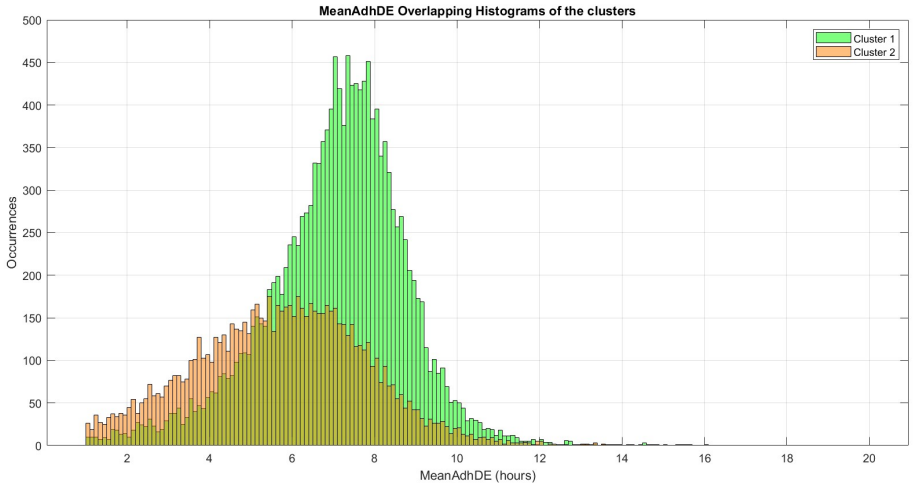


Figure 3.22: Overlapping histograms showing the distribution of MeanAdhDE across the three clusters obtained through single-threshold clustering.

The graph in Figure 3.22 illustrates the distribution of the MeanAdhDE variable across the two clusters identified through the single-threshold method. This overlapping histogram provides a qualitative visualization of how mean adherence in December is spread within the two clusters. A difference in both the mean value and standard deviation of MeanAdhDE can be observed between the clusters, highlighting a distinction in mean adherence patterns. Cluster 1, with lower

adherence variance in January, shows a higher mean adherence in December, whereas Cluster 2 displays lower overall mean adherence in December.

Longitudinal analysis

An additional longitudinal analysis was conducted on the clusters obtained through the single-threshold method, focusing on how adherence outcomes and treatment quality evolved based on how many months (out of the three analyzed: January, June, and December) a patient remained in the low-variance adherence cluster.

The diagram in Figure 3.23 illustrates the methods (explained in Section 2.6.1) used to create 4 clusters. Initially, patients were divided into clusters by applying the ROC-determined threshold to the adherence variance in January (VarAdhJA). These clusters were then further divided based on the same threshold applied to June (VarAdhJU) and finally to December (VarAdhDE). This subdivision resulted in "sub-sub-clusters," which were subsequently merged into four distinct groups: 3 (out of 3) months spent in cluster1, 2 months spent in cluster1, 1 month spent in cluster1 and 0 months spent in cluster1.

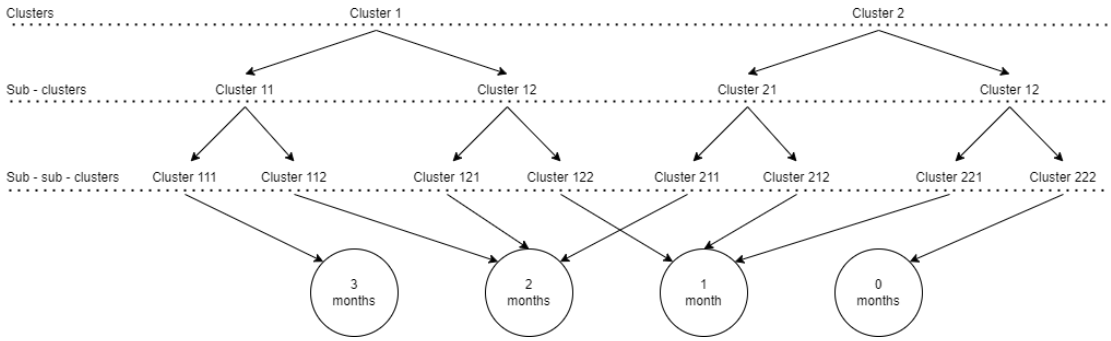


Figure 3.23: Diagram illustrating the sub-cluster generation process based on adherence variance across three months: January (JA), June (JU), and December (DE). Patients were grouped into clusters according to how many months they remained in the low-variance adherence cluster.

For each of these four clusters, the following outcomes were characterized: MeanAdhDE (mean adherence in December), %Adh4DE (percentage of patients meeting the adherence criterion in December), and %CCDE (percentage of patients achieving optimal treatment quality in December). Figure 3.24 presents the results of this analysis. The error bars indicate standard deviations, and statistical significance is denoted by asterisks above the bars.

From this bar plot, patients who remained in the low-variance cluster for all three

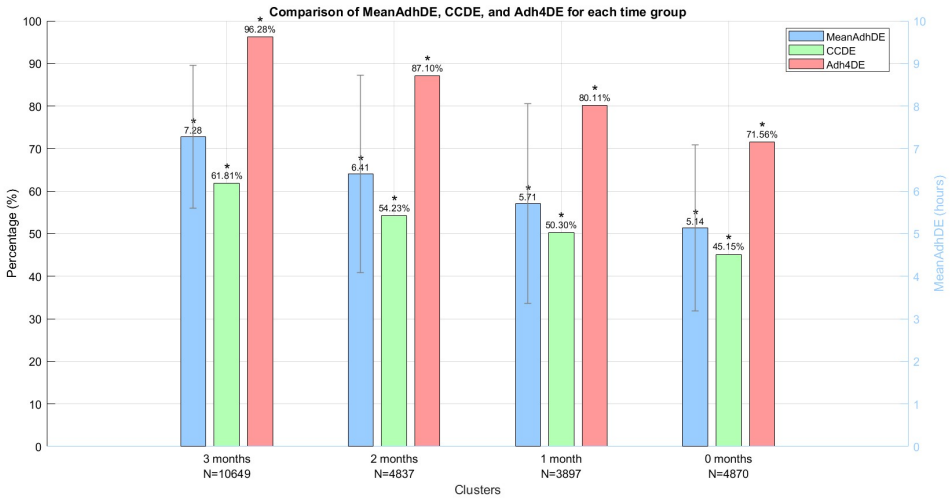


Figure 3.24: Comparison of adherence and treatment quality outcomes across the four clusters, defined by how many months the patients remained in the low-variance adherence cluster. The blue bars represent the MeanAdhDE (mean adherence in December), green %CCDE (optimal treatment quality), and red %Adh4DE (adherence criterion met). Error bars represent standard deviation, and statistical significance is indicated by asterisks.

months (cluster "3 months") demonstrated the highest adherence outcomes, with MeanAdhDE reaching 7,28 hours, %Adh4DE 96,28% and %CCDE 61,81%. As the number of months spent in the low-variance cluster decreased, these values consistently declined, with the "0 months" cluster showing the lowest outcomes: MeanAdhDE of 5.14 hours, 45.15% for %CCDE, and 71.56% for %Adh4DE. All the variables (%Adh4DE, %CCDE, and MeanAdhDE) showed statistically significant differences across the clusters.

These results underscore the importance of maintaining low adherence variance across multiple months to achieve optimal treatment outcomes.

3.6 Summary

This section presents the rationale behind the methodological choices that ultimately shaped the final results.

This study aimed to explore the variability in CPAP adherence among OSAS patients, using telemonitoring data to identify patterns that could predict long-term adherence and treatment quality. The overall goal was to address a clinical

challenge in managing the vast amount of data generated by CPAP devices and to help focus healthcare resources on patients with a higher risk of non-adherence.

OSAS is a disorder characterized by repeated airway obstructions during sleep, leading to interrupted breathing and sleep fragmentation. CPAP therapy is the gold standard for treating moderate-to-severe OSAS, but its effectiveness is heavily dependent on patient adherence. The challenge in clinical practice is managing the large volume of alerts and data from telemonitoring systems, which often overwhelm physicians. This research set out to find a new, quantifiable variable that could help stratify patients based on their adherence behaviors, focusing on the variance in CPAP usage over time.

To achieve this objective, an analysis was conducted using a large French telemonitoring database of patients undergoing CPAP therapy with the ResMed S10 device during the months of January, June, and December 2021. The primary focus was on characterizing the monthly variance in CPAP usage, with particular emphasis on the variance in January, and its relationship to treatment outcomes calculated from the data in December.
The analysis aimed to assess the ability of this newly introduced feature—the monthly variance in adherence (VarAdh)—to effectively stratify patients into distinct clusters based solely on their adherence behavior. Furthermore, the study explored the predictive power of VarAdh for long-term outcomes, evaluating whether this single variable could reliably predict adherence and good quality treatment (needing less attention from physicians).

In order to refine the dataset and ensure meaningful analysis, several inclusion criteria were established. These criteria were designed to eliminate incomplete or inconsistent data and focus on patients whose adherence patterns were representative of the target population. Specifically, criteria such as complete data across all three months, valid demographic information, and adherence below 24 hours per day were applied to maintain data reliability. Additionally, a key criterion requiring a minimum monthly adherence in January of 2 hours was added after consulting with clinicians and comparing the results between Table 3.6 and Table 3.7 . This was crucial to ensure that the patients included in the study had meaningful CPAP usage, as those with low adherence may not qualify for reimbursement and are less likely to experience significant treatment benefits.
Tables 3.7 and 3.8, which compared correlation coefficients for seven and eight inclusion criteria, were pivotal. By adding an eighth criterion (minimum monthly adherence in January of 2 hours), the correlation between adherence variance and key outcomes increased significantly, particularly for VarAdh. This suggests that patients with MeanAdhJA below two hours exhibited patterns that diverged significantly from the overall trend captured by the correlation coefficient.

After establishing the inclusion criteria, the telemonitoring data underwent preprocessing, paying special attention to daily residual AHI and leaks values. These metrics are indicators of treatment quality, but inconsistencies—such as measurements recorded during periods of zero CPAP usage— or outliers—such as really high measurements recorded during short periods of CPAP usage— needed to be addressed. A conservative approach was adopted to manage these outliers, it was not reasonable to assume that these values were merely erroneous (given that there is a scarcity of literature on the subject). The results showed a greater presence of outliers was noted when the hours of daily use were low. This phenomenon is likely attributable to the difficulty in hypothesising that the patient is actually asleep in such a brief period of time. Additionally, errors in identifying apnoeas, hypopnoeas or unintentional leaks are amplified in a shorter measurement period, resulting in the alteration of the AHI and the 95th percentile of unintentional leaks calculation, and consequently reducing the precision of these values. In the end a limited impact on overall outcomes is highlighted, likely because the thresholds were set conservatively to account for the possibility of meaningful outliers.

Regarding Table 3.7, in which each cell represents the correlation coefficient calculated between the independent variable (in the columns) and the dependent variable (in the rows) for the database obtained after the application of eight criteria, it is worth focusing on the correlation coefficients of the dependent variables MeanAdhDE, Adh4DE, CCDE, and NullAdhDE. It is evident that for each of these variables, the highest long-term predictive correlation coefficient corresponds to VarAdhJA, except for the dependent variable CCDE, which shows a higher correlation with age. This suggests that the variability in device usage calculated for the month of January (VarAdhJA) is a more powerful predictive tool compared to other variables (such as age, gender, etc.). However, further analyses should be conducted to examine the potential predictive power of VarAdhJA in combination with age information.
Despite having a generally higher predictive power than the other variables, the correlation coefficient values are mostly low (below 0,3), with two notable exceptions: the correlation between VarAdhJA and MeanAdhDE, which is -0,32, indicating a moderate inverse relationship, and the correlation between VarAdhJA and NullAdhDE, which is 0,39, indicating a moderate direct relationship. In contrast, the relationships between VarAdhJA and Adh4DE, as well as between VarAdhJA and CCDE, are weak and inverse (-0.23 and -0.10, respectively). These results suggest that while VarAdhJA holds moderate predictive power for some treatment outcomes, particularly continuous metrics like MeanAdhDE and NullAdhDE, its relationship with binary variables like Adh4DE and CCDE is weaker.

To segment the patient population, hierarchical clustering was used to explore the

divisions within the data. Figure 3.11, which shows the dendrogram from this analysis, revealed that the optimal number of clusters worth studying in detail was three. This exploratory step was crucial for understanding the structure of the dataset and setting up the subsequent K-means clustering analysis. It provided a clear starting framework for grouping patients based on their January monthly adherence.

Following the hierarchical clustering analysis, K-means clustering was applied, and Tables 3.19 and graph 3.21 highlighted the key characteristics of the resulting clusters.
From the table 3.19, it is possible to observe that the p-values calculated are almost all statistically significant (with the exception of MeanAhi and Ahi5JA), which indicates that at least one cluster significantly differs from the others. Additionally, it can be noted that, for most variables, all three clusters are statistically different from each other (as indicated by the symbols within each cell), with some exceptions. For instance, no significant differences are observed between Clusters 2 and 3 for the variable gender, between Clusters 1 and 3 for MeanLeaks in both June and December, between Clusters 1 and 2 for Leaks24, and only between Clusters 1 and 3 for Ahi5. This highlights that the distinction between Cluster 1 and the other two clusters was significant and warranted further investigation. The characterization of the variables related to residual leaks and AHI consistently shows that these metrics have limited power and significance in distinguishing patient clusters. This suggests that residual AHI and leaks might not be as informative as other variables in predicting adherence patterns and treatment quality. Therefore, further investigations should be conducted to better understand these data and their potential role in patient stratification.
Therefore, the variable of greatest interest, MeanAdhDE, and its distribution within the different clusters was visualized in Figure 3.21. The overlap between Clusters 2 and 3 is evident and it is the reason why it was decided to investigate a further method that studied more thoroughly the difference between Cluster 1 and the other two by combining them. The decision was taken not to pursue the application of the K-means algorithm with two clusters only, due to the discrepancy between the identified threshold (considering only two clusters) and the threshold between Clusters 1 and 2 (considering three clusters).

This led to the decision to explore an alternative approach—using a single-threshold method based on Receiver Operating Characteristic (ROC) curve analysis. This method aimed to identify the optimal threshold for dividing patients into two distinct clusters (adherent and not adherent in December) based on adherence variance, while maximizing Youden's Index to ensure both sensitivity and specificity. The results, as highlighted by the ROC curve in Table 3.15, reconfirmed the

significance of the threshold (Th1) that separates Cluster 1 from Cluster 2 in the K-means analysis (Figure 3.12, reinforcing the importance of this division as the most meaningful cutoff point for stratifying patients based on their adherence.
The third method, utilizing the single-threshold approach, thus provided strong validation for the importance of the Th1 threshold in distinguishing between patients with consistently high adherence (Cluster 1) and those with lower or more variable adherence (Clusters 2 and 3). By applying this threshold, clinicians can reduce the population of patients requiring intensive attention during treatment by excluding those in Cluster 1, who exhibit low variability in device usage at the beginning of the year.

The graph in Figure 3.22 illustrates the distribution of the MeanAdhDE variable across the two clusters identified through the single-threshold method. This overlapping histogram provides a qualitative visualization of how mean adherence in December is spread within the two clusters. A difference in both the mean value and standard deviation of MeanAdhDE can be observed between the clusters, highlighting a distinction in mean adherence patterns. Cluster 1, with lower adherence variance in January, shows a higher mean adherence in December, whereas Cluster 2 displays lower overall mean adherence in December.

The final analysis aimed to quantify the importance of a patient's continued presence in Cluster 1 throughout the year. The graph in Figure 3.24 shows the three primary outcomes—MeanAdhDE, CCDE, and Adh4DE—in relation to the number of months patients remained in Cluster 1, ranging from 0 months to 3 months. The analysis was conducted using the data from January, June, and December, which were available in the database.
From this bar plot, it is clear that patients who remained in the low-variance cluster for all three months (cluster "3 months") demonstrated the highest adherence outcomes, with MeanAdhDE reaching 7,28 hours, %Adh4DE 96,28%, and %CCDE 61,81%. As the number of months spent in the low-variance cluster decreased, these values consistently declined, with the "0 months" cluster showing the lowest outcomes: a MeanAdhDE of 5,14 hours, 45,15% for %CCDE, and 71,56% for %Adh4DE.
All the variables (%Adh4DE, %CCDE, and MeanAdhDE) showed statistically significant differences across the clusters, indicating that a patient's adherence patterns, and thus their overall treatment quality, improve when they consistently remain in the low-variance cluster throughout the year.

Chapter 4

Discussion

4.1 Principal Findings

To the best of our knowledge, this is the first study depicting adherence variance as associated with high adherence and high-quality treatment. A low monthly adherence variance (below 3.2) consistently correlates with a higher likelihood of achieving high mean monthly adherence and high-quality treatment, defined as daily CPAP usage for more than 5 hours, low leak levels (95th percentile leaks <24 L/min), and a low apnea-hypopnea index (AHI <10/h), as identified by the CPAP device. Moreover, the longer patients maintain a low monthly adherence variance, the greater the proportion of time they experience high-quality treatment.

Eguchi et al. [44] analyzed a small population of 219 CPAP-treated patients and suggested that the standard deviation of daily usage duration over a week possibly correlates with poor CPAP adherence. Similarly, Turnbull et al. [45] found that early patterns of CPAP usage were predictive of long-term CPAP use.

These findings raise three key questions: what are the reasons for the association between adherence variance and high treatment quality? What is the significance of adherence variance? How could this new marker be applied in CPAP telemonitoring?

An explanation of this association could be that adherence variance reflects the behaviour of the patients in their life in general. Behaviour could explain the way the patients use their device (e.g. regularity of the use) and how long they use it. Among the possible explanations, it can be hypothesized that a patient who maintains regular sleep/CPAP usage patterns also tends to adhere more carefully to their therapeutic regimen. Low variance in adherence is associated with better treatment quality. It is well known that irregular sleep is linked to greater cardiovascular comorbidity, and the opposite is also true [54, 55, 56]. It is well

established from both cardiovascular [57] and non-cardiovascular [58] clinical trials that adherence per se, including adherence to placebo, is associated with markedly improved health outcomes, an effect that is often substantially larger than that of active therapy. Conversely, regarding non-invasive ventilation, a well-adjusted, comfortable treatment with minimal leaks or residual respiratory events promotes good quality of sleep [59], regular use without nocturnal awakenings, which can otherwise provide opportunities to discontinue the use of non-invasive ventilation.

The interest in adherence variance lies in its simplicity for calculation and interpretation. The precision of this metric also allows for the differentiation of populations with significative different median adherence, significative different median leak rates but a large overlapping. Men, who are known to have higher adherence rates under CPAP compared to women [60] were slightly more frequent in cluster 1 compared to the other clusters.

The use of this new metric in telemonitoring should help focus attention on patients with higher adherence variance, to better understand the causes of this irregularity in use. Clearly, promoting regular use and encouraging regular sleep in these patients should be a priority during therapeutic education sessions. Moreover, a telemonitoring alert threshold for adherence variance around 3 in patients under cpap could be set to trigger physical or tele-interventions.

4.2 Limitations

This study offers valuable insights into the predictive potential of monthly adherence variance in CPAP therapy, but several limitations must be considered when interpreting the results.

One of the primary limitations lies in the lack of consideration for potential confounding factors and the interaction between multiple variables. Specifically, the study does not account for how variables such as age, sex, or other clinical characteristics may influence adherence variance or its predictive power. This could lead to bias in the results, as the ability of the monthly adherence variance quantified in January to stratify patients may not be entirely independent of these other variables. It is possible that some of the predictive power attributed to adherence variance could be partially explained by factors such as age or sex, which were not thoroughly explored in this analysis. Consequently, the threshold applied to adherence variance cannot be considered fully independent of other patient characteristics, nor can it serve as a comprehensive summary of the patient's adherence behavior. This limitation suggests that monthly adherence variance

alone may not be sufficient for a definitive classification of patients.

Another significant limitation is the lack of information on how many years the therapy has been in use and the pressure settings applied during treatment. Patients in the dataset did not all start their therapy at the same time, and although information about how many years the therapy has been in use was available for a small percentage of patients, it was not included as a variable in the analysis due to its limited availability. This lack of data may influence the adherence variance (VarAdh) observed in the study and could introduce bias into the final results and conclusions. Additionally, the pressure settings used during therapy play a critical role in the accuracy of measurements related to leaks and residual AHI, as demonstrated in previous studies (see Section 2.2.1). Incorporating pressure settings in future analyses would be beneficial, as it would enable a more precise evaluation of outliers and distinguish between actual outliers and erroneous values. Moreover, more literature is needed to comprehensively evaluate the accuracy of the ResMed S10 device used for telemonitoring in detecting residual AHI and leaks. A thorough comparison between the measurements of this device and ground truth values obtained through polysomnography would help assess the potential dependence of the device's accuracy on variables such as pressure or mask type.

4.3 Future Developments

To address the limitations identified in this study, further research will be conducted to enhance the methodology and obtain more comprehensive data. Specifically, efforts will be made to request the missing information regarding the number of years of CPAP usage and the pressure settings from the database providers. Acquiring these additional data will enable two key improvements in the analysis.

First, it will refine the technique used for evaluating outliers in residual AHI and leak measurements. Incorporating the pressure settings into the analysis will provide a more accurate method for distinguishing between actual outliers and erroneous or non accurate values, as pressure influences the precision of these measurements. With better outlier understanding, the dataset will reflect more reliable combined criteria metrics to quantify the quality of the treatment, ultimately improving the study's conclusions about VarAdh abilities.

Second, a more structured approach will be applied to study the relationships between different variables and assess the potential biases they may introduce. By incorporating variables such as age, sex, pressure, and years of CPAP use, it will be possible to quantify the independence of the monthly adherence variance

(VarAdh) from these factors. The goal will be to determine whether VarAdh retains its predictive power and ability to stratify patients when controlling for these confounding variables. To achieve this, an advanced method such as Inverse Probability of Treatment Weighting (IPTW) will be employed. IPTW allows for balancing the influence of confounding variables, thereby enabling a more accurate assessment of VarAdh's impact on adherence and treatment outcomes.

The objective of this refined analysis will be to identify a threshold for VarAdh that can be used independently in clinical practice. A clinically applicable threshold would allow physicians to stratify patients based on their adherence behavior without needing to account for multiple variables simultaneously. This would simplify the interpretation of telemonitoring data, making it easier to identify patients at risk of poor adherence and those in need of additional support.

In summary, by incorporating the missing data and employing more robust analytical methods, future iterations of this study will aim to strengthen the conclusions drawn from the current research.

Chapter 5

Conclusions

In conclusion, this study demonstrates an association between a new variable (adherence variance) and high adherence/high-quality treatment.

The interest in adherence variance lies in its simplicity for calculation and interpretation. The precision of this metric also allows for the differentiation of populations with median adherence that might otherwise seem similar.

The use of this new metric in telemonitoring should help focus attention on patients with higher adherence variance, to better understand the causes of this irregularity in use. Clearly, promoting regular use and encouraging consistent sleep in these patients should be a priority during therapeutic education sessions. Moreover, a telemonitoring alert threshold for adherence variance in patients under CPAP therapy could be set to trigger physical or tele-interventions.

Bibliography

[1] Katsuhisa Banno and Meir H. Kryger. «Sleep apnea: Clinical investigations in humans». In: *Sleep Medicine* 8 (June 2007), pp. 400–426 (cit. on p. 1).

[2] Michael J. Thorpy. «Classification of Sleep Disorders». In: *Neurotherapeutics* 9 (Oct. 2012), pp. 687–701 (cit. on p. 1).

[3] Susan Redline, Ali Azarbarzin, and Yüksel Peker. «Obstructive sleep apnoea heterogeneity and cardiovascular disease». In: *Nature Reviews Cardiology* 20 (Aug. 2023), pp. 560–573 (cit. on pp. 1, 4–7).

[4] David G. Rempel, Josiah Sparks, and Benjamin Davies. *Obstructive Sleep Apnea*. Last Update: December 5, 2023. StatPearls Publishing, 2023. URL: `https://www.ncbi.nlm.nih.gov/books/NBK459252/` (cit. on p. 2).

[5] Matthew Ball, Mohammad Hossain, and Devang Padalia. *Anatomy, Airway*. Updated 2023 Jul 25. StatPearls Publishing, 2024. URL: `https://www.ncbi.nlm.nih.gov/books/NBK459258/` (cit. on p. 2).

[6] PDQ Screening and Prevention Editorial Board. *PDQ Oral Cavity, Oropharyngeal, Hypopharyngeal, and Laryngeal Cancers Prevention*. https://www.cancer.gov/types/hea and-neck/patient/oral-prevention-pdq.[PMID: 26389257]. National Cancer Institute. Bethesda, MD (cit. on p. 3).

[7] Alexander V. Zinchuk, Michael J. Gentry, and Joseph Concato. «Phenotypes in obstructive sleep apnea: a definition, examples and evolution of approaches». In: *Sleep Medicine Reviews* 35 (2017), pp. 113–123 (cit. on p. 3).

[8] Yayan Subramani, Matthew Singh, and Jennifer Wong. «Understanding phenotypes of obstructive sleep apnea: applications in anesthesia, surgery, and perioperative medicine». In: *Anesthesia and Analgesia* 124 (2017), pp. 179–191 (cit. on p. 3).

[9] Cheryl R. Laratta, Najib T. Ayas, Marcus Povitz, and Sachin R. Pendharkar. «Diagnosis and treatment of obstructive sleep apnea in adults». In: *Canadian Medical Association Journal* 189 (Dec. 2017), E1481–E1488 (cit. on pp. 4, 8–10).

[10] Vishesh K. Kapur, Dennis H. Auckley, Susmita Chowdhuri, and David C. Kuhlmann. «Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An American Academy of Sleep Medicine Clinical Practice Guideline». In: *Journal of Clinical Sleep Medicine* 13 (Mar. 2017), pp. 479–504 (cit. on pp. 4, 7).

[11] Mohamed El Shayeb, Leigh-Ann Topfer, Tania Stafinski, and Lawrence Pawluk. «Diagnostic accuracy of level 3 portable sleep tests versus level 1 polysomnography for sleep-disordered breathing: a systematic review and meta-analysis». In: *Canadian Medical Association Journal* 186 (Jan. 2014), E25–E51 (cit. on p. 4).

[12] Lu Liu, Yi Wang, Liqiong Hong, and Nicola L. Bragazzi. «Obstructive Sleep Apnea and Hypertensive Heart Disease: From Pathophysiology to Therapeutics». In: *Reviews in Cardiovascular Medicine* 24 (Dec. 2023), p. 342 (cit. on p. 5).

[13] Michael J. Sateia. «International Classification of Sleep Disorders-Third Edition». In: *Chest* 146 (Nov. 2014), pp. 1387–1394 (cit. on p. 7).

[14] Ying Y. Zhao, Jia Weng, and Daniel R. Mobley. «Effect of Manual Editing of Total Recording Time: Implications for Home Sleep Apnea Testing». In: *Journal of Clinical Sleep Medicine* 13 (Jan. 2017), pp. 121–126 (cit. on p. 8).

[15] Lalee Varghese, Grace Rebekah, Priya N, and Ashwin Oliver. «Oxygen desaturation index as alternative parameter in screening patients with severe obstructive sleep apnea». In: *Sleep Science* 15 (Mar. 2022), pp. 224–228 (cit. on p. 8).

[16] Murray W. Johns. «A New Method for Measuring Daytime Sleepiness: The Epworth Sleepiness Scale». In: *Sleep* 14 (Nov. 1991), pp. 540–545 (cit. on p. 8).

[17] Le Wang, Dong-hui Wei, Jing Zhang, and Jie Cao. «Time Under 90% Oxygen Saturation and Systemic Hypertension in Patients with Obstructive Sleep Apnea Syndrome». In: *Nature and Science of Sleep* 14 (Nov. 2022), pp. 2123–2132 (cit. on p. 8).

[18] Miguel A. Martinez-Garcia, Manuel Sánchez-de-la-Torre, David P. White, and Ali Azarbarzin. «Hypoxic Burden in Obstructive Sleep Apnea: Present and Future». In: *Archivos de Bronconeumología* 59 (Jan. 2023), pp. 36–43 (cit. on p. 8).

[19] Diane C. Lim, Diego R. Mazzotti, and Kate Sutherland. «Reinventing Polysomnography in the Age of Precision Medicine». In: *Sleep Medicine Reviews* 52 (Aug. 2020) (cit. on p. 9).

[20] Roohi A. Kaleelullah and Preethi P. Nagarajan. «Cultivating Lifestyle Transformations in Obstructive Sleep Apnea». In: *Cureus* 12.12 (Dec. 2020) (cit. on pp. 10, 12).

[21] Meir H. Kryger, Thomas Roth, and William C. Dement. «The Tongue-Retaining Device: Efficacy and Side Effects in Obstructive Sleep Apnea Syndrome». In: *Sleep Medicine* 10.8 (Aug. 2009), pp. 835–841 (cit. on p. 10).

[22] John W. Lee, Kenneth Sutherland, and David S. Clark. Surgical Therapy of Obstructive Sleep Apnea: A Review. In: vol. 14. 5. Oct. 2012, pp. 383–392 (cit. on p. 11).

[23] Tyler Cooper, Ahmed S. Sufyan, and Salah Aboubakr. *Hypoglossal Stimulation Device*. Ed. by StatPearls Publishing. StatPearls Publishing, Jan. 2024 (cit. on p. 12).

[24] Brian W. Rotenberg, Dorian Murariu, and Kenny P. Pang. «Trends in CPAP adherence over twenty years of data collection: a flattened curve». In: *Journal of Otolaryngology - Head & Neck Surgery* 45.1 (Aug. 2016), p. 43 (cit. on p. 12).

[25] Francesco Baratta, Daniele Pastori, and Tommaso Bucci. «Long-term prediction of adherence to continuous positive air pressure therapy for the treatment of moderate/severe obstructive sleep apnea syndrome». In: *Sleep Medicine* 43 (June 2018), pp. 66–70 (cit. on p. 12).

[26] Jean-Louis Pépin, Sébastien Bailly, and Pierre Rinder. «CPAP Therapy Termination Rates by OSA Phenotype: A French Nationwide Database Analysis». In: *Journal of Clinical Medicine* 10.5 (Mar. 2021), p. 936. DOI: 10.3390/jcm10050936 (cit. on pp. 12, 13, 30, 42).

[27] Bernie Y. Sunwoo, Matthew Light, and Atul Malhotra. «Strategies to augment adherence in the management of sleep-disordered breathing». In: *Respirology* 25.4 (Apr. 2020), pp. 363–371 (cit. on pp. 13, 16).

[28] Atul Malhotra, Kimberly L. Sterling, Peter A. Cistulli, and Jean-Louis Pépin. «Dose-response relationship between obstructive sleep apnea therapy adherence and healthcare utilization». In: *American Thoracic Society* 20.6 (June 2023), pp. 891–897 (cit. on pp. 13, 43).

[29] Arnaud Prigent, Thibaut Gentina, and S. Launois. «Télésuivi des patients traités par pression positive continue pour un syndrome d'apnées/hypopnées obstructives du sommeil : proposition d'un arbre décisionnel». In: *Revue des Maladies Respiratoires* 37.7 (Sept. 2020), pp. 550–560 (cit. on pp. 15, 18).

[30] Terri E. Weaver and Ronald R. Grunstein. «Adherence to continuous positive airway pressure therapy: the challenge to effective treatment». In: *Proceedings of the American Thoracic Society* 5.2 (Feb. 2008), pp. 173–178 (cit. on p. 15).

[31] Anders Brostrom, Anna Stromberg, Jan Maartensson, Martin Ulander, Lena Harder, and Eva Svanborg. «Association of Type D personality to perceived side effects and adherence in CPAP-treated patients with OSAS». In: *Journal of Sleep Research* 16.4 (Dec. 2007), pp. 439–447 (cit. on p. 15).

[32] Carol J. Hoy, Marjorie Vennelle, Ruth N. Kingshott, Heather M. Engleman, and Neil J. Douglas. «Can intensive support improve continuous positive airway pressure use in patients with the sleep apnea/hypopnea syndrome?» In: *American Journal of Respiratory and Critical Care Medicine* 159.4 Pt 1 (Apr. 1999), pp. 1096–1100 (cit. on p. 15).

[33] Eileen R. Chasens, Allan I. Pack, Greg Maislin, David F. Dinges, and Terri E. Weaver. «Claustrophobia and adherence to CPAP treatment». In: *Western Journal of Nursing Research* 27.3 (Apr. 2005), pp. 307–321 (cit. on p. 15).

[34] Keir E. Lewis, Lisa Seale, Iona E. Bartle, Alan J. Watkins, and Philip Ebden. «Early predictors of CPAP use for the treatment of obstructive sleep apnea». In: *Sleep* 27.1 (Feb. 2004), pp. 134–138 (cit. on p. 16).

[35] Kelly G. Baron, Timothy W. Smith, Cynthia A. Berg, Laura A. Czajkowski, Heather Gunn, and Christopher R. Jones. «Spousal involvement in CPAP adherence among patients with obstructive sleep apnea». In: *Sleep and Breathing* 15.3 (Sept. 2011), pp. 525–534 (cit. on p. 16).

[36] Thibaut Gentina et al. «Marital quality, partner's engagement and continuous positive airway pressure adherence in obstructive sleep apnea». In: *Sleep Medicine* 55 (2019), pp. 56–61. DOI: 10.1016/j.sleep.2018.12.009 (cit. on p. 16).

[37] Nancy B. Kribbs, Allan I. Pack, Lewis R. Kline, and Philip L. Smith. «Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea». In: *American Review of Respiratory Disease* 147.4 (Apr. 1993), pp. 887–895 (cit. on p. 16).

[38] Rachel D. Wells, Kenneth E. Freedland, and Robert M. Carney. «Adherence, reports of benefits, and depression among patients treated with continuous positive airway pressure». In: *Psychosomatic Medicine* 69.5 (June 2007), pp. 449–454 (cit. on p. 16).

[39] Karthik Balakrishnan, Kathryn T. James, and Edward M. Weaver. «Predicting CPAP use and treatment outcomes using composite indices of sleep apnea severity». In: *Journal of Clinical Sleep Medicine* 12.06 (June 2016), pp. 849–854 (cit. on p. 16).

[40] Amy M. Sawyer, Nalaka S. Gooneratne, Carole L. Marcus, and Dafna Ofer. «A systematic review of CPAP adherence across age groups: clinical and empiric insights for developing CPAP adherence interventions». In: *Sleep Medicine Reviews* 15.6 (Dec. 2011), pp. 343–356 (cit. on pp. 16, 17).

[41] M. Jeffery Mador, Matthew Krauza, and Adnan Pervez. «Effect of heated humidification on compliance and quality of life in patients with sleep apnea using nasal continuous positive airway pressure». In: *Chest* 128 (Oct. 2005), pp. 2151–2158 (cit. on p. 17).

[42] Arnaud Prigent, Clément Blanloeil, Anne-Laure Serandour, Franck Barlet, Frédéric Gagnadoux, and Dany Jaffuel. «A biphasic effect of age on CPAP adherence: a cross-sectional study of 26,343 patients». In: *Respiratory Research* 24.1 (2023), pp. 1–5. DOI: 10.1186/s12931-023-02543-x (cit. on pp. 17, 32).

[43] Arnaud Prigent, Clément Blanloeil, Dany Jaffuel, Anne Laure Serandour, Franck Barlet, and Frédéric Gagnadoux. «Seasonal changes in positive airway pressure adherence». In: *Frontiers in Medicine* 11 (2024). DOI: 10.3389/fmed.2024.1302431 (cit. on p. 17).

[44] Kana Eguchi, Tsutomu Yabuuchi, Masayuki Nambu, Hirofumi Takeyama, Shozo Azuma, Kazuo Chin, and Tomohiro Kuroda. «Investigation on factors related to poor CPAP adherence using machine learning: a pilot study». In: *Scientific Reports* 12.1 (Nov. 2022), p. 19563 (cit. on pp. 17, 18, 62).

[45] Christopher D. Turnbull, Daniel J. Bratton, Sonya E. Craig, Malcolm Kohler, and John R. Stradling. «In patients with minimally symptomatic OSA can baseline characteristics and early patterns of CPAP usage predict those who are likely to be longer-term users of CPAP». In: *Journal of Thoracic Disease* 8.2 (Feb. 2016), pp. 276–281 (cit. on pp. 18, 62).

[46] Alexandra Valentin, Shyam Subramanian, Stuart F. Quan, Richard B. Berry, and Sairam Parthasarathy. «Air leak is associated with poor adherence to autoPAP therapy». In: *Sleep* 34.6 (June 2011), pp. 801–806 (cit. on p. 18).

[47] Jose F. Rodrigues Jr, Sébastien Bailly, and Jean-Louis Pepin. «CPAP adherence assessment via Gaussian mixture modeling of telemonitored apnea therapy». In: *Applied Sciences (Basel)* 12.15 (July 2022), p. 7618 (cit. on p. 19).

[48] Yukiko Ikeda, Takatoshi Kasai, Fusae Kawana, Satoshi Kasagi, Hisashi Takaya, Sugao Ishiwata, and Koji Narui. «Comparison between the apnea-hypopnea indices determined by the REMstar Auto M series and those determined by standard in-laboratory polysomnography in patients with obstructive sleep apnea». In: *Internal Medicine* 51.20 (Oct. 2012), pp. 2877–2885 (cit. on p. 27).

[49] Hsin-Chia C. Huang, David R. Hillman, and Nigel McArdle. «Control of OSA during automatic positive airway pressure titration in a clinical case series: predictors and accuracy of device download data». In: *Sleep* 35.9 (Sept. 2012), 1277–83A (cit. on p. 27).

[50] Bharati Prasad, David W. Carley, and James J. Herdegen. «Continuous positive airway pressure device-based automated detection of obstructive sleep apnea compared to standard laboratory polysomnography». In: *Sleep and Breathing* 14.2 (June 2010), pp. 101–107 (cit. on p. 27).

[51] Hongzhi Wang, Mohamed J. Bah, and Mohamed Hammad. «Progress in outlier detection techniques: A survey». In: *IEEE Access* 7 (2019), pp. 107964–108000 (cit. on p. 27).

[52] Frédéric Gagnadoux, Emilie Bequignon, Arnaud Prigent, Jean-Arthur Micoulaud‡ Franchi, Juliette Chambe, Joëlle Texereau, Sarah Alami, and Frédéric Roche. «The PAP-RES algorithm: Defining who, why and how to use positive airway pressure therapy for OSA». In: *Sleep Medicine Reviews* 75 (June 2024), p. 101932 (cit. on pp. 30, 43).

[53] Richard J. Schwab, Safwan M. Badr, Lawrence J. Epstein, and Peter Gay. «An official American Thoracic Society statement: continuous positive airway pressure adherence tracking systems. The optimal monitoring strategies and outcome measures in adults». In: *American Journal of Respiratory and Critical Care Medicine* 188.5 (Sept. 2013), pp. 613–620 (cit. on pp. 30, 31).

[54] Kelsie M. Full, Tianyi Huang, Neomi A. Shah, Matthew A. Allison, Erin D. Michos, Daniel A. Duprez, Susan Redline, and Pamela L. Lutsey. «Sleep irregularity and subclinical markers of cardiovascular disease: The Multi-Ethnic Study of atherosclerosis». In: *J. Am. Heart Assoc.* 12.4 (Feb. 2023), e027361 (cit. on p. 62).

[55] Barbara K. Parise et al. «Sleep irregularity and the association with hypertension and blood pressure levels: the ELSA-Brasil study». In: *J. Hypertens.* 41.4 (Apr. 2023), pp. 670–677 (cit. on p. 62).

[56] Hannah Scott et al. «Sleep irregularity is associated with hypertension: Findings from over 2 million nights with a large global population sample». In: *Hypertension* 80.5 (May 2023), pp. 1117–1126 (cit. on p. 62).

[57] Bradi B. Granger et al. «Adherence to candesartan and placebo and outcomes in chronic heart failure in the CHARM programme: double-blind, randomised, controlled clinical trial». In: *Lancet* 366.9502 (Dec. 2005), pp. 2005–2011 (cit. on p. 63).

[58] Jeffrey R. Curtis et al. «Placebo adherence, clinical outcomes, and mortality in the women's health initiative randomized hormone therapy trials». In: *Med. Care* 49.5 (May 2011), pp. 427–435 (cit. on p. 63).

[59] Francesco Fanfulla, Monica Delmastro, Angela Berardinelli, Nadia D'artavilla Lupo, and Stefano Nava. «Effects of different ventilator settings on sleep and inspiratory effort in patients with neuromuscular disease». In: *Am. J. Respir. Crit. Care Med.* 172.5 (Sept. 2005), pp. 619–624 (cit. on p. 63).

[60] Sanjay R. Patel, Jessie P. Bakker, Christy J. Stitt, Mark S. Aloia, and S. Mehdi Nouraie. «Age and sex disparities in adherence to CPAP». In: *Chest* 159.1 (Jan. 2021), pp. 382–389 (cit. on p. 63).