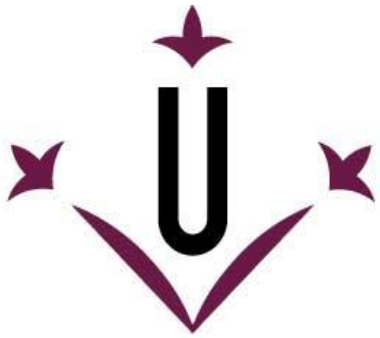
A new approach to obstructive sleep apnoea management

Cecilia Turino



Universitat de Lleida

TESIS DOCTORAL

A NEW APPROACH TO OBSTRUCTIVE SLEEP APNOEA MANAGEMENT

Cecilia Turino

Memoria presentada para optar al grado de Doctor
por la Universidad de Lleida
Programa de Doctorado en Salud

Director

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Tutor

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Dr. Ferran Barbé Illa, professor catedràtic de la Universitat de Lleida, com a director del treball de Tesi Doctoral “A new approach to Obstructive Sleep Apnoea Management ”, realitzat per Cecilia Turino,

CERTIFICO

Que en el treball presentat per optar al Grau de Doctor de la Universitat de Lleida, s'han assolit els objectius fixats a l'inici de la Tesi els quals han estat realitzats en el Departament de Medicina de la Universitat de Lleida. La memòria que es presenta proposa una nova visió global per a la personalització del tractament i seguiment dels pacients amb Síndrome d'Apnea Obstructiva del Son. Per tant, considero apte aquest treball per procedir a la seva lectura i defensa davant la comissió corresponent.

Per a que així consti, signem la present certificació a Lleida a 27 de Juny del 2021.

La presente tesis doctoral se estructura según las directrices de la normativa para la presentación de tesis doctorales en formato de artículos, aprobada por el Acuerdo núm. 67/2014 de la Junta de Gobierno de 10 de abril de 2014 de la Universitat de Lleida.

Los estudios presentados en la presente tesis pertenecen a una misma línea de investigación iniciada en 2017 y dirigida a profundizar en el conocimiento del impacto del Síndrome de Apneas Obstructivas del Sueño (SAOS) sobre la salud general y a la investigación de metodologías innovadoras para el manejo global de los pacientes con SAOS. Los resultados obtenidos han dado lugar a tres artículos publicados en revistas internacionales y a un trabajo cuyos resultados pretenden ser publicados próximamente.

Jordi de Batlle, **Cecilia Turino,** Alicia Sánchez-de-la-Torre, Jorge Abad, Joaquín Duran-Cantolla, R. Douglas McEvoy, Nick A. Antic, Olga Mediano, Valentín Cabriada, Maria José Masdeu, Joaquín Teran, Joan Valls, Ferran Barbé and Manuel Sánchez-de-la-Torre on behalf of the Spanish Sleep Group

"Predictors of obstructive sleep apnoea in patients admitted for acute coronary syndrome"

European Respiratory Journal 2017 Mar 15;49(3):1600550. Factor de Impacto 16.671

Cecilia Turino, Sandra Bertran, Ricard Gavaldá, Ivan Teixidó, Holger Woehrle, Montserrat Rué, Francesc Solsona, Joan Escarrabill, Cristina Colls, Anna García- Altés, Jordi de Batlle, Manuel Sánchez de-la-Torre, Ferran Barbé

"*Characterization of the CPAP-treated patient population in Catalonia"*

PLoS One 2017; 12(9): e0185191. Factor de Impacto: 2.776

Cecilia Turino, Jordi de Batlle, Holger Woehrle, Ana Mayoral, Anabel Lourdes Castro-Grattoni , Sílvia Gómez, Mireia Dalmases, Manuel Sánchez-de-la-Torre and Ferran Barbé
"Management of continuous positive airway pressure treatment compliance using telemonitoring in obstructive sleep apnoea ".
European Respiratory Journal 2017 Feb 8;49(2):1601128. Factor de Impacto 16.671

Cecilia Turino, Ivan D Benítez, Xavier Rafael-Palou, Ana Mayoral, Alejandro Lopera, Lydia Pascual, Rafaela Vaca, Anunciación Cortijo, Anna Moncusí-Moix, Mireia Dalmases, Eloisa Vargiu, Jordi Blanco, Ferran Barbé, Jordi de Batlle

"Management and treatment of patients with obstructive sleep apnea using an Intelligent Monitoring System based on machine-learning aiming to improve continuous positive airway pressure (CPAP) treatment compliance: a Randomized Controlled Trial" submitted

En los cuatro estudios, la doctoranda ha sido responsable de todos los aspectos referentes a la metodología de investigación, en particular se ha encargado: el reclutamiento de los pacientes , realización y análisis de la pruebas del sueño y titulaciones de CPAP, seguimiento de los participantes durante el estudio, recopilación de datos, análisis posterior y extracción de conclusiones. La doctoranda ha participado en la realización del sitio web y de la app móvil del cuarto estudio y ha redactado íntegramente todos los manuscritos.

Dr. Ferran Barbé Illa

INDEX

ABBREVIATIONS

OSA : obstructive sleep apnoea

SNA : sympathetic nervous system activity

LV: left ventricular

HF : heart failure

RH: resistant hypertension

AF : atrial fibrillation

PSG: Complete polysomnography

AASM American Academy of Sleep Medicine

CPAP: Continuous Positive Airway Pressure

APAP: auto-adjusting positive airway pressure

AHI: apnoea-hypopnoea index

PLMS: periodic limb movements of sleep

ACS: acute coronary disease

ICTs: information and communication technologies

ERS: European Respiratory Society

SEPAR: Spanish Society of Pulmonology and Thoracic Surgery

EMR : electronic medical/health records

CSA: central sleep apnoea

RESUM

Per la seva alta prevalença i les greus conseqüències en la salut global, la Síndrome d'Apnea Obstructiva del Son SAOS (SAOS) representa un problema socioeconòmic.

En pacients amb SAOS l'aplicació de la pressió positiva contínua en la via aèria superior (CPAP) s'ha demostrat eficaç i cost-efectiva i representa el mètode terapèutic de referència. No obstant això, la SAOS es considera una malaltia heterogènia amb múltiples fenotips amb diferents implicacions en la morbiditat i mortalitat cardiovascular i resposta al tractament variable. Per tant, el tractament amb CPAP hauria d'aconsellar-se segons el fenotip dels pacients i la millora clínica esperada. Així doncs, es necessiten noves estratègies per millorar el compliment del mateix tractament.

En el primer article no hem aconseguit crear un model que pogués predir la presència de SAOS entre pacients ingressats per la síndrome coronària aguda. No obstant això, hem identificat algunes variables relacionades amb la SAOS (edat, índex de massa corporal, escala de somnolència d'Epworth, nivells de troponina i consum d'antagonistes de calci) i els majors determinants de patir una SAOS greu (l'edat, l' índex de massa corporal, els nivells de triglicèrids, el pic de troponina i una classe de Killip II o superior).

En el segon article hem elaborat la primera anàlisi per clúster de tota la població de Catalunya tractada amb CPAP i hem definit el perfil general dels pacients SAOS tractats amb CPAP, representat per homes de mitjana edat, amb una alta prevalença d'hipertensió arterial, dislipèmia, diabetis i obesitat. A més, hem identificat sis clústers de pacients amb diferents patrons de comorbiditats, mortalitat i ús dels recursos sanitaris. Aquests clústers de pacients han de considerar-se a l'hora d'aconsellar tractament amb CPAP, amb l'objectiu de distribuir els recursos sanitaris de manera més eficient.

En el tercer article hem presentat el segon assaig clínic aleatoritzat que va avaluar l'efectivitat de la tele-monitorització per a millorar el compliment del tractament amb CPAP, el major per nombre de pacients inclosos i el primer que analitza el cost-efectivitat. La telemedicina va demostrar més cost efectivitat que el maneig tradicional.

Finalment, en el quart article, hem avaluat efectivitat i cost-efectivitat del Sistema Intel·ligent de Monitoratge (MiSAOS) per a millorar el compliment amb CPAP. Hem creat una plataforma web i una aplicació per a mòbil amb l'objectiu d'un maneig global per tele-monitorització resultant el sistema MiSAOS més cost efectiu que el maneig tradicional.

RESUMEN

Debido a su alta prevalencia y las graves consecuencias en la salud global, el Síndrome de Apneas Obstructivas del Sueño (SAOS) representa un problema socioeconómico.

La aplicación de la presión positiva continua en la vía aérea superior (CPAP) se ha demostrado eficaz y coste-efectiva y representa el método terapéutico de referencia. Sin embargo, el SAOS se considera una enfermedad heterogénea con múltiples fenotipos, por lo tanto, el tratamiento con CPAP debería aconsejarse según el fenotipo de los pacientes y la mejoría clínica esperada. Por otro lado, también se necesita nuevas estrategias para mejorar el cumplimento del mismo tratamiento.

En el primer artículo no hemos conseguido crear un modelo que pudiese predecir la presencia de SAOS entre pacientes ingresados por síndrome coronario agudo. Sin embargo, hemos identificado algunas variables relacionadas con el SAOS (edad, índice de masa corporal, escala de somnolencia de Epworth, niveles de troponina y consumo de antagonistas de calcio) y unos determinates de padecer un SAOS grave (edad, el índice de masa corporal, los niveles de triglicéridos, el pico de troponina y una clase de Killip II o mayor).

En el segundo artículo hemos realizado el primer análisis por clúster de toda la población de Cataluña tratada con CPAP definiendo el perfil general de los pacientes SAOS tratados con CPAP, resultando ser hombres de mediana edad, con una alta prevalencia de hipertensión arterial, dislipidemia, diabetes y obesidad. Además, hemos identificado seis clústers de pacientes con diferentes patrones de comorbilidades, mortalidad y uso de los recursos sanitarios. Dichos clústers de pacientes tienen que considerarse a la hora de aconsejar tratamiento con CPAP, con el objetivo de distribuir los recursos sanitarios de manera más eficaz.

En el tercer artículo hemos presentado el segundo ensayo clínico aleatorizado que evaluó la efectividad de la telemonitorización para mejorar el cumplimiento del tratamiento con CPAP, el mayor en número de pacientes incluidos y el primero que analiza el coste efectividad. La telemedicina demostró más coste efectividad que el manejo tradicional.

Por último, en el cuarto artículo, hemos evaluado efectividad y coste efectividad del Sistema Inteligente de Monitorización (MiSAOS) para mejorar el cumplimiento con CPAP. Hemos creado una plataforma web y una aplicación para móvil con el objetivo de un control global por telemonitorización encontrando el sistema MiSAOS más coste efectivo que el manejo tradicional.

SUMMARY

Given its high prevalence and repercussions on global health, Obstructive Sleep Apnoea (OSA) is a socioeconomic problem. The application of continuous positive pressure (CPAP) represents the first line and the most cost effective treatment for OSA. However, OSA is now regarded as a heterogeneous disorder characterized by multiple phenotypes with different implications on cardiovascular morbidity, mortality and response to treatment. Thus, CPAP treatment should be recommended according to phenotypes and expected clinical benefit. On the other hand, new methods for improving CPAP compliance are required.

In the first article we failed to create a model that could predict the presence of OSA among patients admitted for coronary artery disease. However, some variables (age, Body Mass Index, the Epworth Sleepiness Scale, peak troponin levels and usual intake of calcium antagonists) were associated with OSA and some others were determinants of severe OSA (age, Body Mass Index, blood triglycerides, peak troponin levels and having a Killip class II or higher)

In the second article, we performed the first cluster analysis involving the entire CPAP-treated population of Catalonia defining a general profile of OSA patients treated with CPAP, being middle-aged men, with a high prevalence of hypertension, dyslipidemia, diabetes and obesity. Furthermore, a cluster analysis identified six patient groups characterized by different patterns of comorbidities, mortality, and healthcare resource use. Such clusters of patients should be taken into account when deciding to treat them, to better distribute healthcare resources.

The third article presented the second randomised controlled clinical trial to assess the effectiveness of telemonitoring for improving CPAP compliance, the largest to date in terms of the number of enrolled patients, and the first to include cost and cost-effectiveness analyses. Telemedicine did not improve CPAP compliance but was more cost effective than traditional follow-up.

Finally, in the fourth article we investigated the effectiveness and cost-effectiveness of the MiSAOS Intelligent Monitoring System for improving CPAP compliance. We created a web platform and a mobile application for patients aiming for global telemonitorized management , finding that MiSAOS is more cost effective than traditional management.

1. INTRODUCTION

1. 1 OBSTRUCTIVE SLEEP APNOEA

Obstructive Sleep Apnoea (OSA) is defined by recurrent episodes of airways obstruction during sleep leading to intermittent hypoxia and sleep fragmentation. OSA is closely related to the appearance of arterial hypertension, cardiovascular and cerebrovascular diseases and represents a risk factor for traffic accidents.

Patients with OSA generally complain of daytime sleepiness due to sleep fragmentation , cognitive impairment and reduced quality of life.

1.2 PATHOGENESIS

OSA is a very prevalent disorder , affecting 15-30% of adults in Western countries [1] and is caused by an increased collapsibility of the upper airways, anatomically extending from the posterior end of the nasal septum to the larynx .

In this zone, the absence of rigid support (bone or cartilage) makes tissues prone to collapse. Patency of upper airways, in fact, exclusively depends on the balance between the forces that promote their closure (neck circumference, intraluminal and extraluminal pressure, pharyngeal wall compliance, and neck circumference) and the forces that are inclined to open them (e.g. dilator muscle activity). The coexistence of unfavorable pharyngeal anatomy and a diminished activity of the upper airway dilator muscles seems to be the principal pathogenetic mechanism of OSA [2]. Furthermore, a high loop gain, (an altered central respiratory pattern generator) , with increased respiratory rhythm oscillation and an extreme ventilatory response to arousals could induce cyclic breathing and promote OSA development [2].

Using magnetic resonance to demonstrate a pharyngeal mucosa edema in OSA patients, the “rostral fluid shift theory” hypotheses that corporal fluids accumulate in the legs due to gravity, whereas in the supine position, fluids redistribute and accumulate in the neck and upper airway. This way, extraluminal pressure in the pharynx increases, eventually exceeding the intraluminal pressure and leading to upper airway collapse [3].

1.3 CLINICAL CONSEQUENCES

The repetitive episodes of airways collapse during sleep cause intermittent hypoxemia and variation of intrathoracic pressure. Both phenomena, along with arousals from sleep to restore airways patency, are responsible for the increased sympathetic nervous system activity (SNA) , augmented oxidative stress and an increased inflammatory state observed in OSA patients [4] that induce endothelial dysfunction and contribute to atherosclerosis and cardiovascular disease development (Fig.1). On the other hand, intermittent hypoxia could directly cause reversible myocardial remodeling in murine models [5] , while the increased SNA induces peripheral vasoconstriction and increased cardiac output that is related to elevations in systemic blood pressure [6].

Furthermore, the increased inspiratory effort during an episode of airways obstruction induces an excessive drop in intrathoracic pressure with increased left ventricular (LV) transmural pressure, and subsequent rise in afterload. At the same time , the drop in thoracic pressure increases venous return, causing right ventricular distention and a leftward shift of the interventricular septum and consequent decreased LV filling [7] . The net result of decreased LV filling and increased afterload is reduced stroke volume. The combination of increased LV afterload and faster heart rate secondary- to augmented SNA leads to myocardial oxygen supply/ demand mismatch, acutely predisposing the patient to cardiac ischemia and arrhythmias, and chronically to LV hypertrophy, LV enlargement, and heart failure (HF).

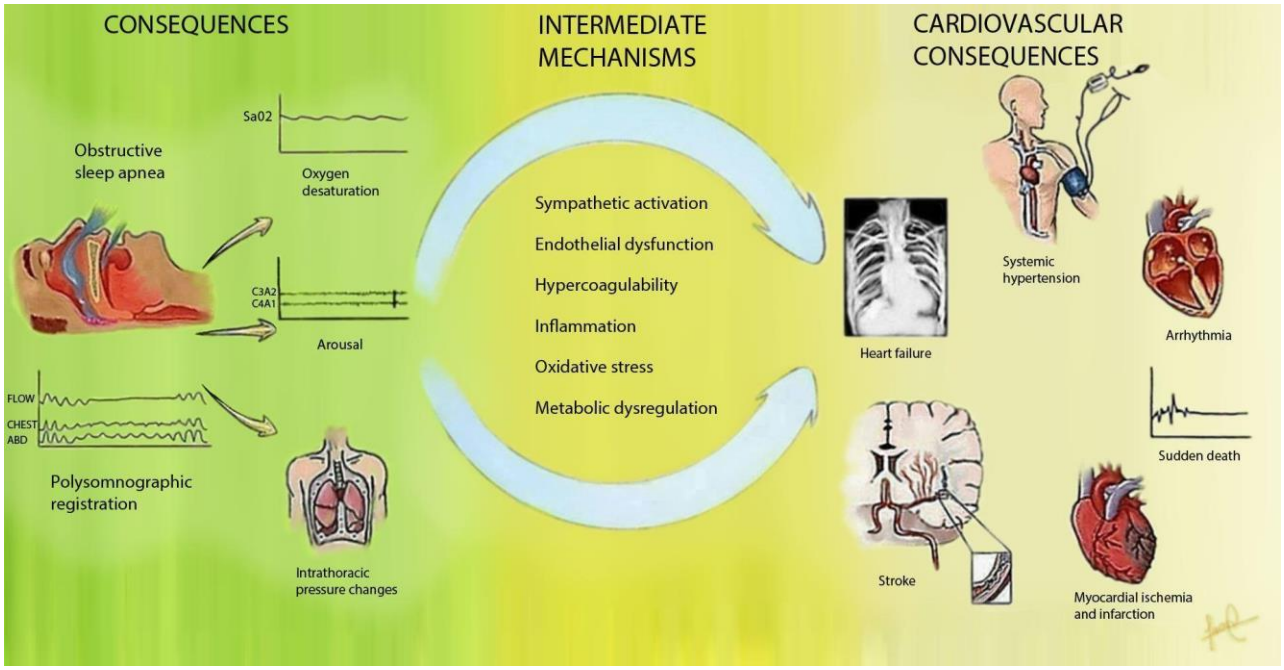

Fig. 1: Repeated arousals, oxygen desaturations and intra-thoracic pressure changes trigger the suspected factors responsible for the cardiovascular consequences of OSA. ***Adapted from Sánchez-de-la-Torre M, Campos-Rodriguez F, Barbé F. Obstructive sleep apnoea and cardiovascular disease Lancet Respir Med. 2013;1:61-72.***

1.4 CLINICAL EVIDENCES

Given the pathophysiological mechanisms that have been discussed , OSA is associated with a broad spectrum of cardiovascular diseases. It is in fact a risk factor for developing hypertension and is a recognized cause of resistant hypertension (RH), being the prevalence of OSA among RH patients of up to 83% [8]. Similarly, OSA patients are at risk for cerebrovascular events, with a linear correlation with OSA severity. OSA is also associated with an increased risk of suffering from ischaemic heart disease and, compared with non-OSA patients,the prevalence of heart failure among OSA is greater than 50% [9].

In addition, OSA patients exhibit increased prevalence of arrhythmias, such as atrial fibrillation (AF), non-sustained ventricular tachycardia, and complex ventricular ectopy, compared with the general population [10]. The frequency of cardiovascular arrhythmias also increases proportionally with increases in OSA severity, and AF recurrence after successful sinus rhythm restoration is more common in OSA patients than in controls [11].

A prognostic value for OSA in outcomes after acute coronary syndrome has also been shown in different studies. In patients with myocardial infarction undergoing a percutaneous coronary intervention, for example, OSA seems to promote atheroma progression, increasing the recurrence of cardiac and cerebrovascular events such as re-infarction, stroke, sudden death and repeated revascularization [12,13].

Nevertheless, OSA is greatly undiagnosed in cardiology settings [14]. It is then of the utmost importance an early identification of sleep respiratory disorder to help to reduce complications.

2. DIAGNOSIS

Complete polysomnography (PSG) represents the GOLD standard for the diagnosis of OSA. However, home testing with portable monitors is also accepted for the diagnosis in patients with high or moderate suspicion of OSA and without comorbidities [15, 16].

Complete PSG allows to identify and score different sleep stages and arousals recording cerebral, muscular and ocular activity by using electroencephalographic and chin electrodes, and two different electrodes placed above the left and right outer canthus, respectively. Oxygen saturation, thoracic and abdominal movements, body position, limb movements and respiratory events are also recorded. Apnea is defined by a drop (> 90%) in the airflow detected by nasal cannula and/or thermistor for at least 10 s. Hypopnea is defined by a reduction in airflow (> 30% and<90%) for at least 10 s, with a drop of at least 3% in the SaO2 and/or arousal from sleep [15]. PSG also supplies information about quality of sleep and presence of sleep disorders other than OSA. Reduced cardiorespiratory polygraphy could detect respiratory events, recording airflow variation, oxygen saturation, cardiac activity, body position and thoracic and abdominal movements. According to te American Academy of Sleep Medicine (AASM), the diagnosis of OSA is confirmed if the number of obstructive events (apneas, hypopneas + respiratory event related arousals, expressed as apnea/hypopnea index, AHI) on PSG is greater than 15 events/hour or greater than 5/hour in a patient who reports symptoms (unintentional sleep episodes during wakefulness; daytime sleepiness; unrefreshing sleep; fatigue; insomnia; waking up breath holding, gasping, or choking; or the bed partner describing loud snoring, breathing interruptions, or both during the patient's sleep).

OSA severity is defined as mild for AHI ≥ 5 and < 15, moderate for AHI ≥ 15 and ≤ 30, and severe for AHI > 30/h [15].

3. TREATMENT

By providing a pneumatic splint, the application of a Continuous Positive Airway Pressure (CPAP) prevents airways collapse and, from its invention till the date, has been representing the GOLD-standard and the first line treatment for symptomatic OSA. A good CPAP compliance (⩾4 h per night for 70% of the nights) [17] has shown to improve daytime sleepiness and patients' quality of life, moderately decrease arterial blood pressure, (mainly in patients with resistant hypertension) [18, 19] and to contribute to reduce the risk of new onset hypertension [20]. Moreover, CPAP, is also an extremely cost-effective therapy, since its correct and constant use is associated with a reduction in healthcare utilization [21]. To determine the optimal pressure level for maintaining upper airway patency and eliminating OSA-related events (apneas, hypopneas, respiratory effort-related arousals, and snoring) a CPAP titration is required. At present, CPAP titration is usually performed at home by auto-adjusting positive airway pressure (APAP) devices and full attended polysomnography (PSG) in the sleep laboratory is only performed in selected patients. Therapeutic pressures for OSA typically fluctuate between 4 and 20 cm H2O. Studies comparing fixed CPAP, APAP, and double-level pressure therapy in OSA have not shown differences in terms of residual AHI, improved quality of life, or decreased daytime sleepiness.

3.1 CPAP : WHO TO TREAT?

Until now, apnoea-hypopnoea index (AHI) , cardiovascular risk and symptoms have been the only tools to suspect, diagnose and grade OSA severity and to plan timing and modality of treatment . Sleepiness and previous history of car crashes due to sleepiness are the only absolute indication for CPAP treatment regardless of severity. In men with severe OSA (AHI > 30) CPAP treatment could reduce the risk of fatal and non-fatal cardiovascular events [22]. On the contrary, in patients with AHI < 30, the presence of symptoms and cardiovascular risk factors should guide treatment

decisions [20, 23-25] . No clear evidence recommends CPAP treatment in patients with mild-to-moderate OSA.

In contrast with this rigid approach to treat it, OSA is now regarded as a very heterogeneous disorder characterized by multiple phenotypes differing in terms of age and gender, symptoms, comorbidities and polysomnographic findings (e.g., severity of hypoxemia and sleep architectural changes).

The analysis of polysomnographic characteristics has allowed to define a predominant REM/non-REM OSA, with an increased cardiovascular risk for REM OSA [26]. Similarly, the assumed sleep body position during respiratory events defines postural OSA, with specific clinical features and treatment options.

Clinical implication of the different OSA phenotypes on cardiovascular morbidity, mortality and response to treatment, has not been completely understood but deepening studies are multiplying. In a recent cluster analysis using polysomnographic data , Zinkhuk et al. found an increased risk of worse prognosis in terms of mortality and cardiovascular events in OSA phenotypes with poor sleep, sleep fragmentation or periodic limb movements of sleep (PLMS).These results were not confirmed using AHI classification alone. Furthermore, the impact of CPAP in reducing mortality and late cardiovascular events was significant only in the 'PLMS' and 'hypopnoea + hypoxia' clusters [27]. Mazzotti et al. found an increased risk of incident of coronary artery disease and heart failure only among the excessively sleepy OSA subtypes [28].

These studies suggest the presence of clusters of patients existing within each of the traditional OSA severity categories defined by AHI, that may have implications for treatment efficacy and cardiovascular events or death.

These different groups probably could also account for the negative results of CPAP treatment in terms of cardiovascular benefits in three big clinical trials and question the benefits of an " indiscriminate" use of CPAP. In the RICCADSA study , a randomized trial in individuals with severe OSA who were not excessively sleepy, no cardiovascular benefit of CPAP in intention to treat analyses was found [29]. Similar results were obtained in the much larger SAVE trial in patients with known cardiovascular diseases and no daytime sleepiness [30].

In the ISAACC study the presence of OSA in non sleepy-patients with acute coronary disease (ACS), was not associated with an increased prevalence of cardiovascular events and treatment with CPAP did not significantly reduce this prevalence [31]. An association between OSA clusters, CPAP adherence and improvement of symptoms under CPAP have been recently addressed, showing a reduced CPAP compliance in patients with concurrent insomnia and OSA, or in those with mild or minimally symptomatic OSA and co-morbidities [32,33].

Given these evidences, it seems now clear the importance of clustering OSA patients considering symptoms, clinical characteristics and comorbidities to evaluate indication and possible benefits from treatment. This is then the first step for a personalized approach and a focused management. At the same time, after establishing which patients phenotypes could maximally benefit from CPAP treatment, new methods of facilitation and improving CPAP compliance are needed, particularly during the first months of treatment when long-term CPAP compliance is established [34] . Up to one third of patients, in fact, underuse or even discontinue CPAP treatment, mostly due to treatment-related side effects (machine noise, pressure intolerance, mask displacement or Claustrophobia) and lack of improvement in symptoms [35]. Many of these problems could be solved by a closer follow-up, allowing patients to continue effective therapy, but this would increase the workload for sleep units and increase the cost of managing OSA. Big Data and Telemedicine could probably represent new tools to implement personalized therapeutic strategies and optimize patient management.

3.2 TELEMEDICINE AND BIG DATA ANALYSIS APPLIED TO SLEEP APNOEA

Telemedicine consists of the use of information and communication technologies (ICTs) (computers, the Internet, and cell phones) to improve patient outcomes by increasing access to care and medical information [36-38]. Telemedicine can be classified as synchronous and asynchronous. Synchronous interactions refer to live interactive telemedicine visits by videoconference or phone calls. Asynchronous telemedicine, on the contrary, refers to interaction where the participants are both separated by distance and by time and includes electronic messaging, remote monitoring and self-care models of care delivery [39].

Although data are not univoque, due to the lack of large randomized multicenter studies with long-term follow-up, telemedicine has already been applied to sleep medicine with promising results and both the European Respiratory Society (ERS) and the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) have encouraged its use in every aspect of OSA management in two recent positionasl papers [40-41] .

New tools applied to smartphones such as sensors for ambient light and respiratory effort, accelerometer for body movement ,microphones for snoring , sensor for oximetry recording, could provide data about sleep waves and sleep apnoea. Furthermore, the new CPAP machines could monitor and record applied pressures, air leaks, the apnoea–hypopnoea index (AHI) and objective adherence and send these information both to patients and healthcare providers, so remote CPAP titration and also patients complete real-time monitoring could be realized with good results [42]. Furthermore , the overall costs of the procedure could be reduced, avoiding the costs of inpatient management and patients' displacement [43].

Spanish guidelines for CPAP treated patients recommend follow-up visits at 1–2 weeks, 1 month and 3 months after CPAP starting [44]. The next visits depend on the patient's characteristics, and CPAP compliance. The early detection of problems and side-effects is of the utmost importance to ensure better compliance, so Telemedicine systems could allow and facilitate appropriate interventions, potentially improving long-term adherence and reducing costs associated with patients' follow-up management.

Kuna et al. reported better compliance for patients with direct access to their own data [45]. Moreover, randomised trials have shown an improvement in CPAP use, when telemonitoring with phone feedback is compared to usual care [46,47] .

Hoet et al. [48] showed that telemonitoring significantly reduced the delay in the first intervention for CPAP treatment (29±25 versus 47±30 days), associated with the detection of problems by the telemonitoring system (39% of patients). Additionally, compliance at 3 months was significantly better in the telemonitoring group (5.7±1.6 versus 4.2±1.9 h·night−1) . Moreover, in a recent trial conducted by Hwang et al. [49] that incorporated automated responses to the patient and education through a web platform (Tele-OSA), telemonitoring was useful in improving short-term compliance (3 months); however, at 1 year of follow-up it was observed that 3 months after the end of telemonitoring interventions compliance to CPAP was similar to that of patients who followed usual management, suggesting that the application of these strategies requires continuous usage. OSA is the only chronic disease for which telemonitoring is available to control objective daily measurements of adherence and efficacy of treatment. The enormous amount of data derived from telemonitoring could be classified as Big Data and could be used to define OSAS phenotypes and to predict response to treatment and for a personalized management of patients.

Big Data identifies large data sets that, due to their complexity and high heterogeneity, cannot be analyzed with conventional techniques (e.g., multivariate regression analyses) but require particular computational efforts ("big data analytics") to be effectively managed and integrated, in order to extract information on trends, interactions, and associations. Big Data is described by five 'Vs' signifying Volume, Velocity, Variety, Veracity and Value, referring to a massive quantity of data, its speed of acquisition, the diversity and heterogeneity of data sources. Big Data sets regarding OSA could now be obtained from electronic medical/health records (EMR), medical administrative data, health insurance claims and cohorts and registries [50-52] and also from the social media and web or mobile app [53-55].

One advantage of CPAP continuous telemonitoring is the availability of repeated measures of the residual apnoea–hypopnoea index and leaks every night. Using a large population-based data set generated by CPAP devices, Liu et al. highlight the dynamic nature of central sleep apnoea (CSA) occurring during CPAP treatment identifying several different clinical phenotypes [56]. Previous studies in this field with relatively small sample sizes and heterogeneous populations provided inconsistent results, partly explained by the titration procedures [57]. On the contrary, this study demonstrated a true prevalence of CSA in the 3.5% of CPAP-treated OSA and its association with older age and discontinuation of therapy [56]. The identification of treatment-emergent CSA by

telemonitoring could facilitate early intervention to reduce the risk of therapy discontinuation and shift to more efficient ventilator modalities.

Given its characteristics of highly prevalent, systemic, multimorbid and chronic disease, OSA requires a combination of long-term home-based treatments. The estimated cost of diagnosing and treating OSA in the US in 2015 was approximately $12.4 billion [58] . A significant part of the cost is assigned to follow-up visits and home care provider services.

Thus, in order to better distribute and use economic resources, Big Data derived from telemonitoring could help to differentiate less complex patient phenotypes, from more complex and comorbid ones on whom concentrate efforts and economic resources.

4. HYPOTHESIS AND OBJECTIVES

Given the characteristics of OSA and its repercussions on global health, a personalized approach to the patients is required. This thesis tries to deepen the knowledge in this direction with four articles, exploring different ways of dealing with this disease, from an early detection of OSA in specific subgroups of patients to a different management of treated patients.

Article 1 "Predictors of obstructive sleep apnoea in patients admitted for acute coronary syndrome"

Hypothesis : identifying undiagnosed obstructive sleep apnoea (OSA) patients in cardiovascular clinics could improve their management.

Objective: given the high prevalence of OSA, the authors propose respiratory polygraphy as a to-be-explored strategy to identify OSA in ACS patients. To build an OSA predictive model, a broad analysis of clinical variables has been performed in a cohort of acute coronary syndrome (ACS) patients.

Article 2 " Characterization of the CPAP-treated patient population in Catalonia"

Hypothesis : the identification of the different OSA phenotypes is important in defining prognosis and guiding the therapeutic strategy.

Objective : to characterise the entire population of CPAP treated patients in Catalonia and to identify specific patient profiles using cluster analysis.

Article 3 " Management of continuous positive airway pressure treatment compliance using telemonitoring in obstructive sleep apnoea"

Hypothesis: CPAP is an effective treatment for obstructive sleep apnoea, but treatment compliance is often unsatisfactory.

Objective : to assess the efficacy and cost-effectiveness of telemonitoring for improving CPAP compliance.

Article 4 “Management and treatment of patients with obstructive sleep apnea using an Intelligent Monitoring System based on machine-learning aiming to improve continuous positive airway pressure (CPAP) treatment compliance: a Randomized Controlled Trial “

Hypothesis : information and communication technologies (ICTs) have been applied to sleep medicine with promising results in terms of improving CPAP treatment compliance.

Objective : to investigate the effectiveness and cost-effectiveness of the MiSAOS Intelligent Monitoring System for improving CPAP compliance.

5. SCIENTIFIC ARTICLES

5.1 ARTICLE 1

"Predictors of obstructive sleep apnoea in patients admitted for acute coronary syndrome "

Jordi de Batlle, **Cecilia Turino**, Alicia Sánchez-de-la-Torre, Jorge Abad, Joaquín Duran-Cantolla, R. Douglas McEvoy, Nick A. Antic, Olga Mediano, Valentín Cabriada , Maria José Masdeu, Joaquín Teran, Joan Valls, Ferran Barbé and Manuel Sánchez-de-la-Torre on behalf of the Spanish Sleep Group.

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Predictors of obstructive sleep apnoea in patients admitted for acute coronary syndrome

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Given the high prevalence of OSA in patients suffering ACS, respiratory polygraphy should be routinely performed http://ow.ly/tmKE306wyDc

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ABSTRACT Identifying undiagnosed obstructive sleep apnoea (OSA) patients in cardiovascular clinics could improve their management. Aiming to build an OSA predictive model, a broad analysis of clinical variables was performed in a cohort of acute coronary syndrome (ACS) patients.

Sociodemographic, anthropometric, life-style and pharmacological variables were recorded. Clinical measures included blood pressure, electrocardiography, echocardiography, blood count, troponin levels and a metabolic panel. OSA was diagnosed using respiratory polygraphy. Logistic regression models and classification and regression trees were used to create predictive models.

A total of 978 patients were included (298 subjects with apnoea–hypopnoea index (AHI) <15 events·h^{-1} and 680 with AHI ⩾15 events·h^{-1}). Age, BMI, Epworth sleepiness scale, peak troponin levels and use of calcium antagonists were the main determinants of AHI ⩾15 events·h^{-1} (C statistic 0.71; sensitivity 94%; specificity 24%). Age, BMI, blood triglycerides, peak troponin levels and Killip class ⩾II were determinants of AHI ⩾30 events·h^{-1} (C statistic of 0.67; sensitivity 31%; specificity 86%).

Although a set of variables associated with OSA was identified, no model could successfully predict OSA in patients admitted for ACS. Given the high prevalence of OSA, the authors propose respiratory polygraphy as a to-be-explored strategy to identify OSA in ACS patients.

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Introduction

Cardiovascular diseases represent the main cause of death worldwide, with 17.5 million victims in 2012 [1]. Coronary artery disease (CAD) is responsible for more than half of all cardiovascular deaths, and acute coronary syndrome (ACS), ranging from unstable angina to myocardial infarction, is often the first manifestation of underlying CAD [1, 2]. Obstructive sleep apnoea (OSA), defined as the presence of repetitive episodes of upper airway collapse during sleep, is a common chronic condition, affecting 10% of middle-aged men and 3% of middle-aged women [3]. Increased sympathetic activity and oxidative stress induced by recurrent airway obstruction, intermittent hypoxaemia and arousals from sleep, cause endothelial dysfunction and predispose patients to atherosclerosis [4]. OSA is widely recognised as a risk factor for cardiovascular diseases [5, 6] and increasing evidence suggests a key role and a prognostic value of OSA in ACS.

The prevalence of OSA is very high amongst patients with CAD, affecting from 57 to 79% of patients hospitalised for ACS [7–9]. Furthermore, several authors have observed worse cardiovascular outcomes when OSA coexists with ACS [10]. In patients with myocardial infarction undergoing a percutaneous coronary intervention, for example, OSA seems to promote atheroma progression, increasing the recurrence of cardiac and cerebrovascular events such as re-infarction, stroke, sudden death and repeated revascularisations [10–13]. Among such complex patients, the early identification and treatment of those with OSA may help to reduce these complications. Unfortunately, OSA remains greatly underdiagnosed in cardiology settings [14, 15].

Few studies to date have tried to predict the risk of suffering from OSA among patients with acute coronary syndrome using clinical variables. Furthermore, all of them have focused on a limited number of clinical variables [16, 17]. Using data from the Impact of sleep apnoea syndrome in the evolution of acute coronary syndrome cohort (ISAACC), we performed a broad analysis of multiple clinical variables in a large cohort of ACS patients, with the aim of identifying the main determinants of OSA in such a group of patients.

Methods

Study population

This is an ancillary study of the ISAACC study, which is a multicentre, open-label, parallel, prospective, randomised, controlled trial (registered trial NCT01335087), evaluating the effect of continuous positive airway pressure (CPAP) treatment on the incidence of new cardiovascular events in patients with an episode of ACS and OSA [18]. Starting in June 2011, patients admitted for ACS to coronary care units or cardiology hospitalisation wards at 14 teaching hospitals in Spain (male and females aged $\geqslant$18 years) were evaluated regards their suitability for the trial [18]. All patients underwent respiratory polygraphy during the first 48–72 h after admission. Patients with an apnoea–hypopnoea index (AHI) >15 events·h^{-1} and $\leqslant$50% of central apnoeas were randomised to conservative or CPAP treatment. Those patients with an AHI $\leqslant$15 events·h^{-1} were considered controls. For the current study, we used information about the first 1000 patients recruited consecutively in the ISAACC study, excluding patients with more than 50% of missing variables. We assessed individual predictors for OSA and developed predictive models to determine the pre-test probability of OSA based on a broad range of baseline variables in non-sleepy ACS patients, thus using the results of the respiratory polygraphy as the outcome variable.

Acute coronary syndrome was defined as the acute presentation of coronary disease with or without ST elevation infarction, unstable angina, or type 1 MI [19]. The exclusion criteria for the current study included the following: previous treatment with CPAP; psychophysical inability to complete questionnaires; the presence of any previously diagnosed sleep disorder; patients with >50% central apnoeas or the presence of Cheyne–Stokes respiration, daytime sleepiness (Epworth Sleepiness Scale (ESS) >10), patients with chronic diseases (*e.g.* neoplasms, renal insufficiency (glomerular filtration rate <15 mL·min^{-1}·1.73 m^{-2}), severe chronic obstructive pulmonary disorder (a forced expiratory volume in 1 s <50%), chronic depression and other limiting chronic diseases), a medical history that could interfere with the study objectives, any processes, whether cardiovascular or otherwise, that reduce life expectancy to <1 year, and patients in cardiogenic shock.

The ethics committee of each participating centre approved the study (approval number in the coordinator centre: 2010-852), and all patients provided written informed consent.

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Conflict of interest: Disclosures can be found alongside this article at erj.ersjournals.com

Data collection

Outcomes

OSA diagnosis was based on the results of overnight cardio-respiratory polygraphy, which is in accordance with the guidelines of the Spanish national consensus on apnoea–hypopnoea syndrome [20]. All participating centres used the same model of polygraph (Embletta; ResMed, Bella Vista, Australia). Nasal pressure airflow, thoracoabdominal movements, electrocardiography and pulsioxymetry were recorded. Obstructive apnoea was defined as an absence of airflow lasting ⩾10 s in presence of abdominal and thoracic movements. Central apnoeas were defined in absence of both thoracic and abdominal wall movement and airflow lasting ⩾10 s. Obstructive hypopnoea was defined as a reduction in airflow lasting ⩾10 s associated with oxygen desaturation in presence of both thoracic and abdominal movements. Oxygen desaturation was defined as a decrease in arterial oxygen saturation ⩾4%. Respiratory polygraphy studies were performed without supplemental oxygen. The AHI was defined as the number of episodes of apnoea and hypopnoea per hour of recording. OSA was defined as an AHI >15 events·h^{-1} with ⩽50% of central apnoeas; and severe OSA as an AHI >30 events·h^{-1} with ⩽50% of central apnoeas. A minimum of 3 h of satisfactory signal recording were required to consider the test as valid.

Covariates

Sociodemographic variables as well as information regarding lifestyle habits, clinical background and usual pharmacological treatment were recorded using questionnaires. The degree of self-reported sleepiness/drowsiness was analysed by the Spanish version of the Epworth Sleepiness Scale (ESS) test [21]. Quality of life was assessed with the EuroQol EQ-5D questionnaire. Anthropometric measures included weight, height, body mass index (BMI), neck, waist and hip circumferences, and the waist-to-hip ratio. Blood pressure measures, electrocardiography and echocardiography were routinely performed during patient admission. Similarly, variables related to ACS severity (ejection fraction, Killip classification, number of affected vessels, number of stents implanted and peak troponin) and short-term prognosis (length of stay in the coronary unit, length of hospitalisation, complications and mortality) were measured during patient admission. Killip classification is a clinical scale that uses physical examination to define the severity of ventricular dysfunction after a cardiac ischaemic event, predicting the risk of death, and ranging from class I (absence of heart failure signs) to class 4 (cardiogenic shock) [22]. Fasting blood samples were obtained and analysed including a complete blood count and a basic metabolic panel.

Statistical analyses

Data for each participant were uploaded to a database. Only the coordinating centre (Hospital Arnau de Vilanova and Santa Maria, IRBLleida, Lleida, Spain) had full access to the database. Given the heterogeneity of troponin measurement methods among centres, method-specific deciles of peak troponin were computed and an overall troponin variable grading from 1 to 10 was created for each subject. The mean±SD, median (interquartile range) or frequency (%) were computed to evaluate the differences between OSA and control patients, assessing the significance of such differences with the Chi-squared test, t-test or Mann–Whitney test, as appropriate.

Multiple imputation techniques were used to estimate values for those patients with missing variables. Multiple imputation was implemented under the assumption that the missing data were missing at random. For each missing value, ten imputed values were generated on the basis of AHI, sex, age and reported hypertension, dyslipidaemia and diabetes. This was generated using multiple imputation by chained equations, specifying the univariate imputation model appropriate for each variable, using "mi impute chained" command in Stata (StataCorp, College Station, TX, USA), version 12.1. Crude logistic regression models were used to identify potential determinants of OSA. R^2 using Fisher's z over imputed data and C statistic over imputed data were used to identify variables with predictive value for OSA. Top 20 variables according to R^2 were considered for multivariate logistic regression models. After a first multivariate model including all selected variables, variables with p>0.100 were removed from the model. In a subsequent final model, only significant variables were kept. Potential interactions among such variables were tested. Predictive value of the final model was assessed in terms of R^2 using Fisher's z over imputed data and C statistic over imputed data. The same methodology was applied to assess predictors for severe OSA (AHI >30 events·h^{-1}). Additionally, sensitivity analyses excluding subjects with more than 20% of missing variables were performed.

Classification and regression trees (CART) [23] were also used as alternatives to the previously mentioned logistic regression approach to assess OSA and severe OSA. Briefly, CART provide top-down set of hierarchical variables with specified cutoff points which classify all subjects according to their probability of having OSA. Therefore, an inverted tree structure is generated, with each node corresponding to a variable and a given cutoff point, and with each dead-end branch providing the probability of such subjects having OSA. Sensitivity, specificity and predictive value of CART were assessed. CART methods were used before any multiple imputations. CART analyses were performed using the R statistical package.

Data analysis was conducted using Stata 12.1 (StataCorp, College Station, TX, USA). The threshold for significance was set at 0.05.

Results

A total of 978 patients were included in the analysis, after the exclusion of 22 patients with more than 50% of missing data. Up to 298 patients had AHI <15 events·h^{-1} and 680 had AHI ⩾15 events·h^{-1} (379 with AHI ⩾30 events·h^{-1}). The main cardio-respiratory polygraphy variables of the cohort's subjects are shown in table 1.

Tables 2, 3 and online supplementary table S1 show all the characteristics of the ISAACC patients that were considered as potential determinants of OSA, according to AHI. The tables include information about anthropometric variables, biological determinants, usual pharmacological treatment, clinical background and lifestyle habits, cardiovascular variables and hospitalisation-related variables. OSA patients were significantly older than controls (p<0.001). Similarly, OSA patients were significantly more obese than controls according to weight (p<0.001), body mass index (p<0.001), neck circumference (p<0.001) and waist and hip circumferences (p<0.001). Other very significant differences were found for peak troponin (p<0.001), blood glucose (p=0.005), use of calcium antagonist (p=0.001), hypertension (p=0.001) and the Epworth Sleepiness Scale (p=0.001), for which OSA patients showed increased values.

After computing R^2 using Fisher's z over imputed data and C statistic over imputed data to identify variables with the highest predictive value for OSA, the top 10 variables were BMI (R^2=0.054), weight (R^2=0.037), waist (R^2=0.035), hip (R^2=0.030) and neck (R^2=0.016) circumferences, age (R^2=0.011), peak troponin (R^2=0.010), calcium antagonists (R^2=0.010), Epworth sleepiness scale (R^2=0.009) and hypertension (R^2=0.009). The final logistic regression models attempting to predict subjects with an AHI ⩾15 events·h^{-1}, as well as their prediction capacity according to R^2 and the C statistic are shown in table 4. The adjusted model had a C statistic of 0.71, with a sensitivity of 94.1% and a specificity of 24.3%. Similarly, table 5 shows the final logistic regression models attempting to predict severe OSA. The adjusted model had a C statistic of 0.67, with a sensitivity of 30.5% and a specificity of 85.5%. Age, BMI and the ESS were common variables to both OSA and severe OSA models. Given the poor predictive capacity of the developed models, no validation studies were performed. Sensitivity analyses excluding subjects with more than 20% of missing values reported very similar results and did not increase the predictive capacity of the models.

The use of CART did not provide better prediction capacity. Briefly, the first nodes of the classification tree for AHI ⩾15 events·h^{-1} involved BMI, age and ESS, while for AHI ⩾30 events·h^{-1} included BMI, prothrombin time and peak troponin levels. The former model had a sensitivity of 95% and a specificity of 43% while the later had a sensitivity of 53% and a specificity of 87%. Overall, none of the resulting classification trees had a good enough performance to justify a validation study.

Discussion

In this ancillary study including 978 non-sleepy subjects from the ISAACC trial with an episode of ACS, we measured a broad range of clinical variables and assessed their association to OSA. At the same time, we tried to develop a predictive model, which could be used to identify ACS patients who should be referred for a sleep study. Age, BMI, the ESS, peak troponin levels and usual intake of calcium antagonists were the main determinants of having AHI ⩾15 events·h^{-1}. Similarly, we identified age, BMI, blood triglycerides, peak troponin levels and having a Killip class II or higher as the main determinants of AHI ⩾30 events·h^{-1}.

In accordance to previous literature, we found age, BMI and the ESS to be strongly associated with OSA [16, 17, 24]. However, no associations for sex were found although being previously reported [25]. Intake of one of the most widely used antihypertensive drugs, calcium antagonists, was also related to OSA, thus indicating an association between OSA and hypertension in our cohort. Additionally, we found higher

TABLE 1 Cardio-respiratory polygraphy results of the ISAACC patients according to apnoea–hypopnoea index (AHI)

	AHI		p-value#
	<15 events·h^{-1}	⩾15 events·h^{-1}	
Patients n	298	680	
AHI events·h^{-1}	6 (3–10)	32 (22–46)	<0.001
Oxygen desaturation index >4% h^{-1}	5 (2–10)	26 (16–42)	<0.001
Mean $Sa0_2$ %	92.7±4	92.0±4	0.018
Minimum $Sa0_2$ %	84.4±11	81.0±10	<0.001
Time with $Sa0_2$ <90% %	0.6 (0–6.1)	4.3 (0.9–19)	<0.001

Data are presented as mean±SD or median (interquartile range), unless otherwise stated. $Sa0_2$: arterial oxygen saturation; AHI: apnoea–hypopnoea index. #: t-test or Kruskal–Wallis test as appropriate.

TABLE 2 Baseline characteristics of the ISAACC patients according to apnoea–hypopnoea index (AHI)

	AHI		p-value[#]
	<15 events·h^{-1}	⩾15 events·h^{-1}	
Patients n	298	680	
General characteristics			
Age years	58±12	60±11	<0.001
Males n (%)	246 (83)	564 (83%)	0.881
Body mass index kg·m^{-2}	27.0±4	29.5±5	<0.001
Epworth Sleepiness Scale	4.9±2.5	5.4±2.5	0.001
Biological determinations			
Hematocrit %	42.5±5	41.8±5	0.046
Glucose mg·dL^{-1}	102 (87–134)	109 (93–142)	0.005
Triglycerids mg·dL^{-1}	137.5±83	146.8±77	0.132
Total cholesterol mg·dL^{-1}	181±46	177±43	0.286
Uric acid mg·dL^{-1}	5.5 (4.5–7.2)	6.1 (5–7.2)	0.007
Creatinine mg·dL^{-1}	0.89±0.2	0.92±0.3	0.093
Peak troponin (deciles)[¶]	4 (1–7)	5 (3–8)	<0.001
Creatine phosphokinase UI·mL^{-1}	236 (103–828)	254 (118–844)	0.328
Usual pharmacological treatment			
Diuretics	45 (15)	128 (19)	0.183
β-blockers	73 (25)	149 (22)	0.305
ACE inhibitors	38 (22)	90 (22)	0.943
Angiotensin II receptor antagonists	20 (12)	63 (16)	0.228
Calcium antagonists	19 (7)	92 (14)	0.001
Hypolipidaemics	91 (31)	262 (39)	0.022
Oral antidiabetics	46 (16)	132 (20)	0.158
Insulin	21 (7)	47 (7%)	0.908

Data are presented as mean±SD, n (%) or median (interquartile range), unless otherwise stated. [#]: Chi-squared test, one-way ANOVA or Mann–Whitney test as appropriate; [¶]: test-specific deciles of peak troponin (computed separately for each testing method to account for differences in sensitivity among centres).

peak troponin levels in OSA patients compared to controls. Some studies have also observed increased levels of plasma troponin, a sign of subclinical myocardial injury, in patients with OSA [26–28]. Moreover, a relation between troponin levels and OSA severity has been prudently suggested regardless of concerns involving a potential clustering of cardiovascular risk factors in subjects with OSA [26–28]. Finally, it is noteworthy that although not making it into the final predictive models, blood glucose levels but not diabetes was related to the risk of suffering OSA, probably due to diabetes under-diagnosis [29, 30].

Regarding severe OSA patients, we identified blood triglycerides and the Killip class as the main predictors together with age, BMI and peak troponin levels. The presence of dyslipidaemia in patients suffering OSA has been shown in several studies [31, 32], and the levels of blood triglycerides represent a risk factor for cardiovascular diseases and have a prognostic role among ACS patients [33, 34]. However, Lavie *et al.* [35] did not find differences in triglycerides in patients with and without OSA and CAD. Several trials have shown a worse prognosis in patients with ACS and OSA [10–13, 36]. Nonetheless, no differences in troponin levels were found in a study comparing a small group of patients with CAD and untreated OSA to controls [37]. Similarly, Valo *et al.* [38] studied 21 patients with CAD and OSA without observing any differences with the control group. Finally, a broader study with 136 myocardial infarction patients with and without OSA showed lower levels of troponin among OSA patients, and even a cardio-protective role of OSA suggesting that OSA (or episodic hypoxia) might act as a "preconditioning factor" [39]. However, as acknowledged by the authors of previous studies, small study sample sizes could be the underlying factor explaining many of the contrasting results.

The current study has several strengths including a large sample size, the novelty of the setting in non-sleepy patients with an episode of ACS, and the measurement of a broad range of sociodemographic, anthropometric, lifestyle, biological, clinical, pharmacological and cardiovascular variables, while using respiratory polygraphy to determine OSA status. On the other hand, several limitations should be acknowledged. 1) The study is lacking the dimension of genetics; however, genetic tests are not usually available in standard clinical settings and would hinder the usefulness of the predictive model. 2) No information regarding snoring was collected as such information is not investigated in coronary units.

TABLE 3 Baseline clinical characteristics and variables related to acute coronary syndrome severity of the ISAACC patients according to apnoea–hypopnoea index (AHI)

	AHI		p-value#
	<15 events·h^{-1}	⩾15 events·h^{-1}	
Patients n	298	680	
Clinical background			
Hypertension	125 (42)	362 (53)	0.001
Dyslipidaemia	144 (48)	356 (52)	0.246
Diabetes mellitus	64 (22)	168 (25)	0.274
Cardiomyopathy	69 (23)	145 (22)	0.569
Stroke	7 (2)	25 (4)	0.274
Cardiovascular variables			
First ACS episode	238 (85)	520 (82)	0.199
Anomalies in ECG	233 (90)	518 (91)	0.621
ACS category			
Unstable angina	33 (13)	67 (12)	
Non-STEMI	125 (50)	268 (48)	
STEMI	94 (37)	224 (40)	0.736
Ejection fraction	56.9±10	54.9±11	0.017
Killip Class			0.060
I	221 (95)	497 (90)	
II	11 (5)	47 (8)	
III	0 (0)	6 (1)	
IV	0 (0)	3 (1)	

Data are presented as n (%) or mean±SD, unless otherwise stated. ACS: acute coronary syndrome; ECG: electrocardiogram; STEMI: ST-elevation myocardial infarction. #: Chi-squared test, one-way ANOVA or Mann-Whitney test as appropriate.

3) The exclusion of part of the controls modified the proportion of cases and controls, which ultimately affects the sensitivity and specificity of the predictive models; however, this fact does not diminish the predictive capacity of the models but rather shifts the model from a specificity-driven model toward a sensitivity-driven one. 4) No additional confirmatory polygraphy was available to ensure that fluid accumulation, as a symptom of acute cardiac dysfunction, was not distorting OSA diagnosis; however, polygraphies made in a subset of 57 participants after 1 year showed minor differences in median AHI: 32.0 events·h^{-1} at baseline and 28.7 events·h^{-1} after 1 year, thus suggesting that acute fluid accumulation was unlikely to distort OSA diagnosis. 5) The inclusion in the imputation models of subjects with up to 49% of missing variables could also be seen as a limitation; however, it is well known that analyses including only complete cases are likely to be biased due to substantial loss of precision and power [40]. Moreover, sensitivity analyses including only subjects with up to 19% of missing variables reported very similar results, thus confirming that the current results were not driven by missing values and/or

TABLE 4 Logistic regression models of potential determinants of obstructive sleep apnoea defined as apnoea–hypopnoea index ⩾15 events·h^{-1}

	Crude models				Adjusted model#			
	OR	95% CI	$R^{2¶}$	C statistic+	OR	95% CI	$R^{2¶}$	C statistic+
Age years	1.02	1.01–1.04	0.011	0.57	1.03	1.01–1.04		
Body mass index kg·m^{-2}	1.15	1.11–1.20	0.054	0.67	1.15	1.11–1.20		
Epworth Sleepiness Scale	1.10	1.04–1.16	0.009	0.57	1.08	1.02–1.15		
Calcium antagonists	2.28	1.37–3.81	0.010	0.54	1.91	1.11–3.28		
Peak troponin deciles§	1.08	1.03–1.13	0.010	0.57	1.08	1.03–1.13		
Full model							0.090	0.71

Positive predictive value over imputed data for the adjusted model=73.94%. Negative predictive value over imputed data for the adjusted model=64.50%. #: all covariates are together in a single model. ¶: R^2 using Fisher's z over imputed data; +: C statistic over imputed data; §: test-specific deciles of peak troponin (computed separately for each testing method to account for differences in sensitivity among centres).

TABLE 5 Logistic regression models of potential determinants of severe OSA defined as Apnoea–hypopnoea index ⩾30 events·h^{-1}

	Crude models				Adjusted model[#]			
	OR	95% CI	$R^{2¶}$	C statistic[+]	OR	95% CI	$R^{2¶}$	C statistic[+]
Age years	1.02	1.006–1.03	0.007	0.55	1.03	1.01–1.04		
Body mass index kg·m^{-2}	1.11	1.08–1.15	0.040	0.63	1.11	1.08–1.15		
Triglycerides cg·dL^{-1}	1.03	1.007–1.04	0.007	0.55	1.03	1.01–1.05		
Peak troponin deciles[§]	1.07	1.02–1.11	0.007	0.56	1.07	1.02–1.12		
Killip class >I	2.31	1.39–3.88	0.010	0.53	2.06	1.21–3.52		
Full model							0.072	0.67

Positive predictive value over imputed data for the adjusted model=57.15%. Negative predictive value over imputed data for the adjusted model=66.04%. [#]: all covariates are together in a single model; [¶]: R^2 using Fisher's z over imputed data; [+]: C statistic over imputed data; [§]: test-specific deciles of peak troponin (computed separately for each testing method to account for differences in sensitivity among centres).

imputation technique. 6) The abovementioned strength of using non-sleepy subjects (ESS ⩽10) could also be considered a weakness, as this exclusion handicaps the feasibility of an effective predictive model; however, sleepy subjects tend to be managed in sleep units and thus are not the main target of a hypothetical predictive model. 7) Not having data on the performance of screening questionnaires, such the Berlin questionnaire or the obstructive sleep apnoea in acute coronary syndrome score for the patients with ACS, precluded a comparison between them and the developed models.

This study tried to define the clinical variables that characterise patients hospitalised for ACS at higher risk of undiagnosed OSA, especially when such patients do not show significant daytime sleepiness. As expected, OSA could be suspected in older patients with high BMI and more reported sleepiness even if it would be considered not relevant enough to classify the patient as sleepy. Moreover, regular use of calcium antagonists and higher peak troponin levels, were also associated with a higher risk of OSA. However, grouping these variables into a single predictive model was insufficient to create an effective predictor model for OSA. It could be argued that, as none of the non-sleepy ACS patients are undergoing sleep tests (0% sensitivity and 100% specificity scenario), a predictive model calibrated in order to maximise specificity could be of some use while having a small impact on medical costs. However, such a model would have a poor sensitivity and many OSA patients would never undergo a sleep test. Therefore, options beyond predictive modelling should be explored. In this sense, the broadening application of respiratory polygraphy devices and the reduction in costs associated with domiciliary sleep tests, as well as the potential to-be-demonstrated beneficial effects of CPAP treatment, sleep testing of patients admitted for ACS could be a sound option in the near future.

In conclusion, our study failed to construct a model capable of successfully predicting OSA in patients admitted for ACS, although a set of variables associated with OSA in such patients including age, BMI and ESS but also peak troponin levels and regular use of calcium antagonists was identified. While the clinical value of correctly identifying and managing non-sleepy OSA patients who are admitted to hospital with ACS awaits the results of large randomised controlled trials of OSA treatment such as ISAACC, the authors propose the exploration of a broad use of respiratory polygraphy, rather than clinical variables, to identify OSA in ACS populations.

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References

1 WHO Fact sheet N°317. www.who.int/mediacentre/factsheets/fs317/en/ Date last accessed: July 17, 2015. Date last updated: January 2015.

2 Kumar A, Cannon CP. Acute coronary syndromes: diagnosis and management, part I. *Mayo Clin Proc* 2009; 84: 917–938.
3 Peppard PE, Young T, Barnet JH, *et al.* Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol* 2013; 177: 1006–1014.
4 Sánchez-de-la-Torre M, Campos-Rodriguez F, Barbé F. Obstructive sleep apnoea and cardiovascular disease. *Lancet Respir Med* 2013; 1: 61–72.
5 Gottlieb DJ, Yenokyan G, Newman AB, *et al.* Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. *Circulation* 2010; 122: 352–360.
6 Marin JM, Carrizo SJ, Vicente E, *et al.* Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 2005; 365: 1046–1053.
7 Yumino D, Tsurumi Y, Takagi A, *et al.* Impact of obstructive sleep apnea on clinical and angiographic outcomes following percutaneous coronary intervention in patients with acute coronary syndrome. *Am J Cardiol* 2007; 99: 26–30.
8 Danzi-Soares NJ, Genta PR, Nerbass FB, *et al.* Obstructive sleep apnea is common among patients referred for coronary artery bypass grafting and can be diagnosed by portable monitoring. *Coron Artery Dis* 2012; 23: 31–38.
9 Ben Ahmed H, Boussaid H, Hamdi I, *et al.* Prevalence and predictors of obstructive sleep apnea in patients admitted for acute myocardial infarction. *Ann Cardiol Angeiol (Paris)* 2014; 63: 65–70.
10 Loo G, Tan AY, Koo CY, *et al.* Prognostic implication of obstructive sleep apnea diagnosed by post-discharge sleep study in patients presenting with acute coronary syndrome. *Sleep Med* 2014; 15: 631–636.
11 Saito T, Yoshikawa T, Sakamoto Y, *et al.* Sleep apnea in patients with acute myocardial infarction. *Crit Care Med* 1991; 19: 938–941.
12 Wu X, Lv S, Yu X, *et al.* Treatment of OSA reduces the risk of repeat revascularization after percutaneous coronary intervention. *Chest* 2015; 147: 708–718.
13 Nakashima H, Katayama T, Takagi C, *et al.* Obstructive sleep apnoea inhibits the recovery of left ventricular function in patients with acute myocardial infarction. *Eur Heart J* 2006; 27: 2317–2322.
14 Costa LE, Uchôa CH, Harmon RR, *et al.* Potential underdiagnosis of obstructive sleep apnoea in the cardiology outpatient setting. *Heart* 2015; 101: 1288–1292.
15 Konecny T, Kuniyoshi FH, Orban M, *et al.* Under-diagnosis of sleep apnea in patients after acute myocardial infarction. *J Am Coll Cardiol* 2010; 56: 742–743.
16 Lee CH, Khoo SM, Tai BC, *et al.* Obstructive sleep apnea in patients admitted for acute myocardial infarction. Prevalence, predictors, and effect on microvascular perfusion. *Chest* 2009; 135: 1488–1495.
17 Glantz H, Thunstro E, Herlitz J, *et al.* Occurrence and predictors of obstructive sleep apnea in a revascularized coronary artery disease cohort. *Ann Am Thorac Soc* 2013; 10: 350–356.
18 Esquinas C, Sánchez-de-la Torre M, Aldomá A, *et al.* Rationale and methodology of the impact of continuous positive airway pressure on patients with ACS and nonsleepy OSA: the ISAACC Trial. *Clin Cardiol* 2013; 36: 495–501.
19 Deckers JW. Classification of myocardial infarction and unstable angina: a re-assessment. *Int J Cardiol* 2013; 167: 2387–2390.
20 Spanish National Consensus in Sleep Apnea-Hypopnea Syndrome (SAHS). *Arch Bronconeumol* 2005; 41: s3–11.
21 Chiner E, Arriero JM, Signes-Costa J, *et al.* Validation of the Spanish version of the Epworth Sleepiness Scale in patients with a sleep apnea syndrome. *Arch Bronconeumol* 1999; 35: 422–427.
22 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment Elevation. *Eur Heart J* 2016; 37: 267–315.
23 Breiman L, Friedman JH, Olshen RA, *et al.* Classification and regression trees. Monterey, Wadsworth & Brooks/ Cole Advanced Books & Software, 1984.
24 Szymanski FM, Filipiak KJ, Hrynkiewicz-Szymanska A, *et al.* Clinical characteristics of patients with acute coronary syndrome at high clinical suspicion for obstructive sleep apnea syndrome. *Hellenic J Cardiol* 2013; 54: 348–354.
25 Zhao LP, Tan A, Tai BC, *et al.* Effects of gender on the prevalence of obstructive sleep apnea in patients with coronary artery disease. *J Clin Sleep Med* 2014; 10: 1279–1284.
26 Randby A, Namtvedt SK, Einvik G, *et al.* Obstructive sleep apnea is associated with increased high-sensitivity cardiac troponin T levels. *Chest* 2012; 142: 639–646.
27 Barceló A, Esquinas C, Bauçà JM, *et al.* Effect of CPAP treatment on plasma high sensitivity troponin levels in patients with obstructive sleep apnea. *Respir Med* 2014; 108: 1060–1063.
28 Einvik G, Røsjø H, Randby A, *et al.* Severity of obstructive sleep apnea is associated with cardiac troponin I concentrations in a community-based sample: data from the Akershus Sleep Apnea Project. *Sleep* 2014; 37: 1111–1116.
29 Fraser LA, Twombly J, Zhu M, *et al.* Delay in diagnosis of diabetes is not the patient's fault. *Diabetes Care* 2010; 33: e10.
30 Levetan CS, Passaro M, Jablonski K, *et al.* Unrecognized diabetes among hospitalized patients. *Diabetes Care* 1998; 21: 246–249.
31 Nadeem R, Singh M, Nida M, *et al.* Effect of obstructive sleep apnea hypopnea syndrome on lipid profile: a meta-regression analysis. *J Clin Sleep Med* 2014; 10: 475–489.
32 Iesato K, Tatsumi K, Saibara T, *et al.* Decreased lipoprotein lipase in obstructive sleep apnea syndrome. *Circ J* 2007; 71: 1293–1298.
33 Schwartz GG, Abt M, Bao W, *et al.* Fasting triglycerides predict recurrent ischemic events in patients with acute coronary syndrome treated with statins. *J Am Coll Cardiol* 2015; 65: 2267–2275.
34 Wan K, Zhao J, Huang H, *et al.* The association between triglyceride/high-density lipoprotein cholesterol ratio and all-cause mortality in acute coronary syndrome after coronary revascularization. *PLoS One* 2015; 10: e0123521.
35 Lavie L, Perelman A, Lavie P. Plasma homocysteine levels in obstructive sleep apnea: association with cardiovascular morbidity. *Chest* 2001; 120: 900–908.
36 Glantz H, Thunström E, Johansson MC, *et al.* Obstructive sleep apnea is independently associated with worse diastolic function in coronary artery disease. *Sleep Med* 2015; 16: 160–167.

37 Gami AS, Svatikova A, Wolk R, *et al.* Cardiac troponin T in obstructive sleep apnea. *Chest* 2004; 125: 2097–2100.
38 Valo M, Wons A, Moeller A, *et al.* Markers of myocardial ischemia in patients with coronary artery disease and obstructive sleep apnea: effect of continuous positive airway pressure therapy. *Clin Cardiol* 2015; 38: 462–468.
39 Shah N, Redline S, Yaggi HK, *et al.* Obstructive sleep apnea and acute myocardial infarction severity: ischemic preconditioning? *Sleep Breath* 2013; 17: 819–826.
40 Sterne JA, White IR, Carlin JB, *et al.* Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009; 338: b2393.

5.2 ARTICLE 2

"*Characterization of the CPAP-treated patient population in Catalonia*"

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RESEARCH ARTICLE

Characterization of the CPAP-treated patient population in Catalonia

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Abstract

There are different phenotypes of obstructive sleep apnoea (OSA), many of which have not been characterised. Identification of these different phenotypes is important in defining prognosis and guiding the therapeutic strategy. The aim of this study was to characterise the entire population of continuous positive airway pressure (CPAP)-treated patients in Catalonia and identify specific patient profiles using cluster analysis.

A total of 72,217 CPAP-treated patients who contacted the Catalan Health System (CatSalut) during the years 2012 and 2013 were included. Six clusters were identified, classified as "Neoplastic patients" (Cluster 1, 10.4%), "Metabolic syndrome patients" (Cluster 2, 27.7%), "Asthmatic patients" (Cluster 3, 5.8%), "Musculoskeletal and joint disorder patients" (Cluster 4, 10.3%), "Patients with few comorbidities" (Cluster 5, 35.6%) and "Oldest and cardiac disease patients" (Cluster 6, 10.2%). Healthcare facility use and mortality were highest in patients from Cluster 1 and 6. Conversely, patients in Clusters 2 and 4 had low morbidity, mortality and healthcare resource use.

Our findings highlight the heterogeneity of CPAP-treated patients, and suggest that OSA is associated with a different prognosis in the clusters identified. These results suggest the need for a comprehensive and individualised approach to CPAP treatment of OSA.

Introduction

Obstructive sleep apnoea (OSA) is a chronic disorder characterised by recurrent episodes of upper airway collapse during sleep, and affects 5–14% of adults aged 30–70 years [1]. OSA has been linked with increased rates of morbidity and mortality due to its strong association with hypertension, metabolic, cardiovascular and cerebrovascular diseases, and cancer [2,3]. OSA

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has a negative impact on quality of life, increases the risk of traffic accidents and has an important socioeconomic impact [4,5]. Given these multiple medical and social consequences, OSA could be considered a complex and heterogeneous disorder, deserving of a multidisciplinary approach and personalised treatment. However, there is really only one standard approach to the management of OSA–the application of nocturnal continuous positive airway pressure (CPAP) to splint the upper airways open. CPAP has been shown to improve quality of life and to decrease arterial blood pressure in patients with resistant hypertension [6, 7].

Using distinct types and sources of data, some authors have recently used cluster analysis to identify different phenotypes of OSA patients [8–11]. Cluster analysis allows patients to be grouped according to similar characteristics while maximising differences among different patient groups. Applied to OSA patients, cluster analysis could help to improve knowledge about the condition, confirm known associations with comorbidities, and potentially identify currently unknown associations. In Catalonia, approximately 1% of the general population is currently estimated to be using CPAP. However, there are no clear data on the profiles of OSA patients treated with CPAP, whether there is heterogeneity within this population, and which pathologies or comorbidities might be associated with different patient profiles.

This study characterised the entire CPAP-treated population of Catalonia using cluster analysis in order to define specific profiles based on age, sex, associated comorbidities, mortality and the use of healthcare resources.

Methods

Design, setting and study population

This cross-sectional study was conducted in Catalonia (Spain) based on data from the Agency for Health Quality and Assessment of Catalonia (AQuAS). AQuAS is a public entity working under the auspices of Catalonia's Health Services Department promoting the quality, safety and sustainability of the public Catalan healthcare system. All OSA patients in the Catalan Health Service who were treated with CPAP and had any use of healthcare resources during 2012 and/or 2013 were included in the analysis. Patients receiving CPAP via private health services were excluded because full data were not available. Since all data were anonymised, neither individual patient consent nor ethical approval were required.

Coding and selection of diseases

The International Classification of Disease version 9 (ICD-9) was used for disease coding at each contact with the Catalan Public Health Service (in primary care, hospital or nursing home).

For this study, we selected a combination of the most frequent diagnoses in our dataset and made a list of the most clinically relevant diagnoses (Table 1) [9]. Several diagnoses were grouped in disease categories in order to facilitate information management. To obtain consistent and clinically relevant patterns of association, and to avoid spurious relationships that could bias the results, we considered only diagnoses with a prevalence of $> 1\%$.

Statistical analysis

Descriptive statistics of mean (standard deviation) or median [interquartile range (IQR)] were estimated for quantitative variables with a normal or non-normal distribution, respectively, while absolute and relative frequencies were used for qualitative variables. Normal distribution was analysed using the Shapiro-Wilks test.

Table 1. The most frequent and clinical relevant diagnoses.

Comorbidities	CHARS ICD-9 Diagnosis Code(s)
HIV	042.xx HIV
Malignant neoplasms	140.xx—149.xx Lip, oral cavity and pharynx
	150.xx—159.xx Digestive organs and peritoneum
	160.xx—165.xx Respiratory and intrathoracic organs
	170.xx—176.xx Bone, connective tissue, skin and breast
	179.xx—189.xx Genitourinary organs
	190.xx—199.xx Other locations
	200.xx—208.xx Lymphatic tissues and hematopoietic
Diabetes	250.xx Diabetes mellitus
Dyslipidaemia	272.xx Disorders of lipid metabolism
Obesity	278.xx Overweight, obesity and other types of hyperalimentation
Anaemia	280.xx Anaemia due to iron deficiency
	281.xx Other deficiency anaemia
	282.xx Hereditary haemolytic anaemias
	283.xx Acquired haemolytic anaemias
	284.xx Aplastic anaemia and other medullary insufficiency syndromes
	285.xx Other anaemias and unspecified anaemias
Dementia	290.xx Dementia
Schizophrenic disorders	295.xx Schizophrenic disorders
Mental disorders	296.xx Mood (affective) disorder
	305.xx Drugs without dependence
Anxiety	300.xx Anxiety, dissociative and somatoform disorders
Parkinson's disease	332.xx Parkinson's disease
Hypertension	401.xx Essential hypertension
	402.xx Hypertensive heart disease
	403.xx Chronic hypertensive kidney disease
	404.xx Hypertensive chronic heart and kidney disease
	405.xx Secondary hypertension
Other heart diseases	414.xx Other forms of chronic ischemic heart disease
Dysrhythmia	427.xx Dysrhythmia
Heart failure	428.xx Heart failure
Cerebrovascular diseases	430.xx Subarachnoid haemorrhage
	431.xx Intracerebral haemorrhage
	432.xx Other intracranial haemorrhage and not specified intracranial haemorrhage
	433.xx Stenosis and occlusion of precerebral arteries
	434.xx Occlusion of the brain arteries
	435.xx Transient cerebral ischemia.
	436.xx Poorly-defined acute cerebrovascular disease
	437.xx Other cerebrovascular diseases and other poorly-defined cerebrovascular diseases
	438.xx Late effects of cerebrovascular disease
COPD	490.xx Non specified as acute or chronic bronchitis
	491.xx Chronic bronchitis
	492.xx Emphysema
Asthma	493.xx Asthma
Bronchiectasis	494.xx Bronchiectasis
Pancreatic diseases	577.xx Pancreatic diseases

(*Continued*)

Table 1. (*Continued*)

Comorbidities	CHARS ICD-9 Diagnosis Code(s)
Chronic renal failure	584.xx Chronic renal failure
Chronic nephropathy	585.xx Chronic nephropathy
Prostatic hyperplasia	600.xx Prostatic hyperplasia
Inflammatory arthritis	714.xx Inflammatory arthritis
Osteoarthrosis	715.xx Osteoarthrosis and related disorders
Other joint disorders	719.xx Other joint disorders and unspecified joint disorders
Back disorders	724.xx Other disorders and unspecified back disorders
Musculoskeletal disorders	726.xx Peripheral tendinitis
Joint disorders	729.xx Other soft tissue disorders
Osteoporosis	733.xx Osteoporosis

List of the diagnoses and group of diagnoses used to perform the Multiple Correspondence Analysis (MCA) and the cluster analysis.

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A Multiple Correspondence Analysis (MCA) was used to reduce dimensionality on the studied diagnoses. The number of dimensions obtained by MCA was identified using the Kaiser's criterion and the Scree test. The individual coordinates obtained with MCA were introduced in a k-means cluster analysis. Cluster analysis has been used to describe homogeneous subgroups (clusters) with similar characteristics (intra-cluster distance minimised), but different from other groups (inter-cluster distance maximised). The final number of clusters was defined on the basis of maximising the ratio between intra-cluster and inter-cluster variance, more specifically Calinsky-Harabasz's criterion. The R statistical software, version 3.3.1, was used for all the analyses.

Results

Patient characteristics

Of the 7,478,968 population in Catalonia (2013), 71,217 patients (0.95%) were being treated with CPAP; 70,469 of these used healthcare services (2012–2013) and were included in the analysis (Fig 1). Median age was 64.5 years [IQR57.0; 72.0], 74.9% were men, and 5.29% died during the study period. Median time on CPAP was 34.9 months [IQR 14.8; 58.5]. The most frequent diagnoses were hypertension (61.2%), dyslipidaemia (29.9%), diabetes (29.6%) and obesity (18.3%).

Cluster analysis

Six clusters of CPAP-treated OSA patients were identified. Hypertension and diabetes were present in almost all the clusters among the most frequent comorbidities (Fig 2). The main characteristics of each cluster are summarized in Table 2.

Cluster 1 (Neoplastic patients) included 7,340 patients (10.4%), a high proportion of whom had malignant neoplasm (88.5%), and the mortality rate was high (15.0%). Cluster 2 (Metabolic syndrome patients) included 19,535 patients (27.7%). High proportions of patients in this group had hypertension (84.1%), dyslipidaemia (57.1%), obesity (35.9%) and diabetes (53.9%); mortality was low (1.9%). Cluster 3 (Asthmatic patients) included 4,082 patients (5.8%). This cluster of patients all had asthma, included a high proportion of women (53.0%) and had a low mortality rate (4.8%). Cluster 4 (Musculoskeletal and joint disorders patients)

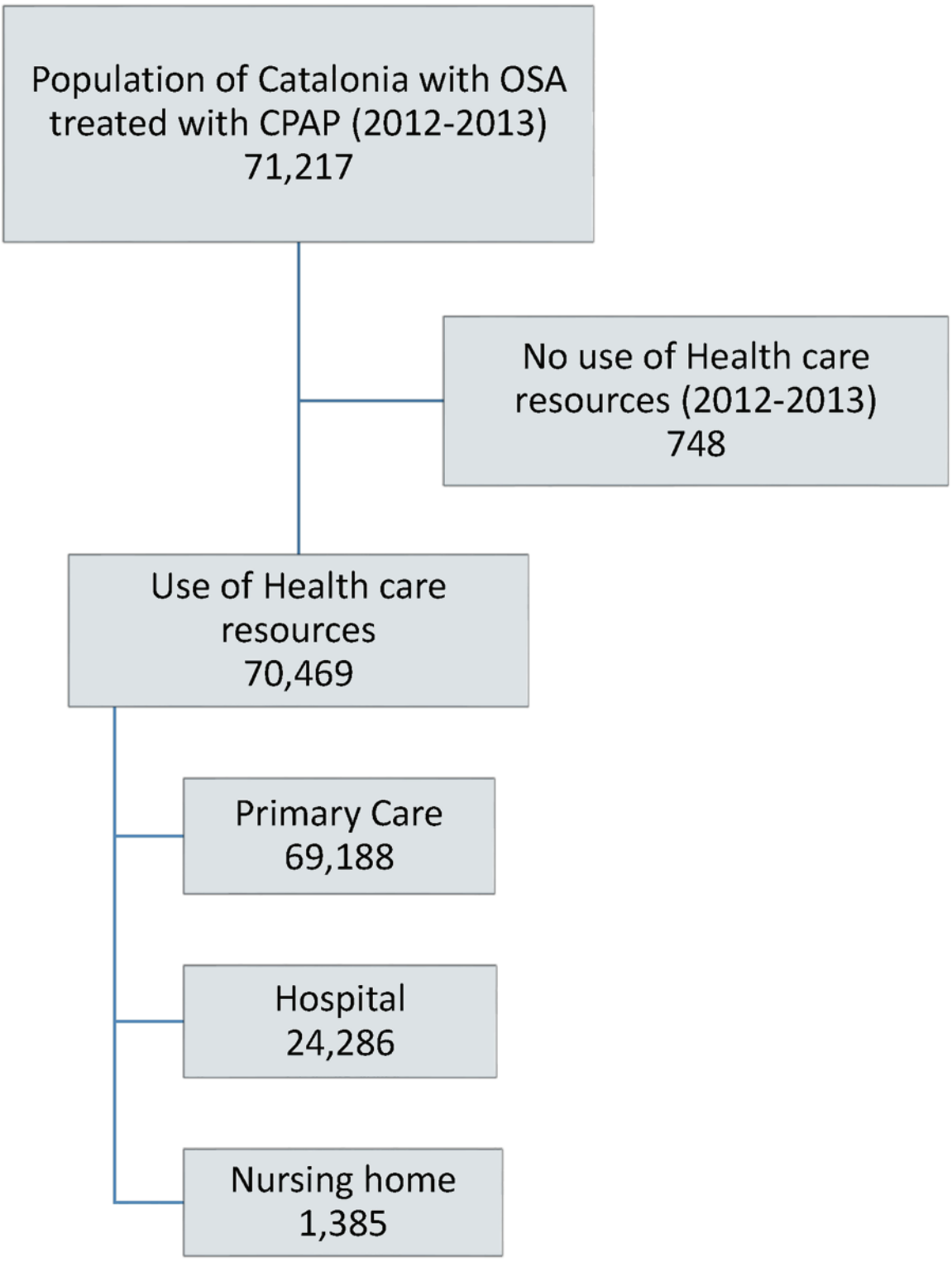

Fig 1. Sampling framework. Abbreviations: OSA, obstructive sleep apnoea; CPAP, continuous positive airway pressure.

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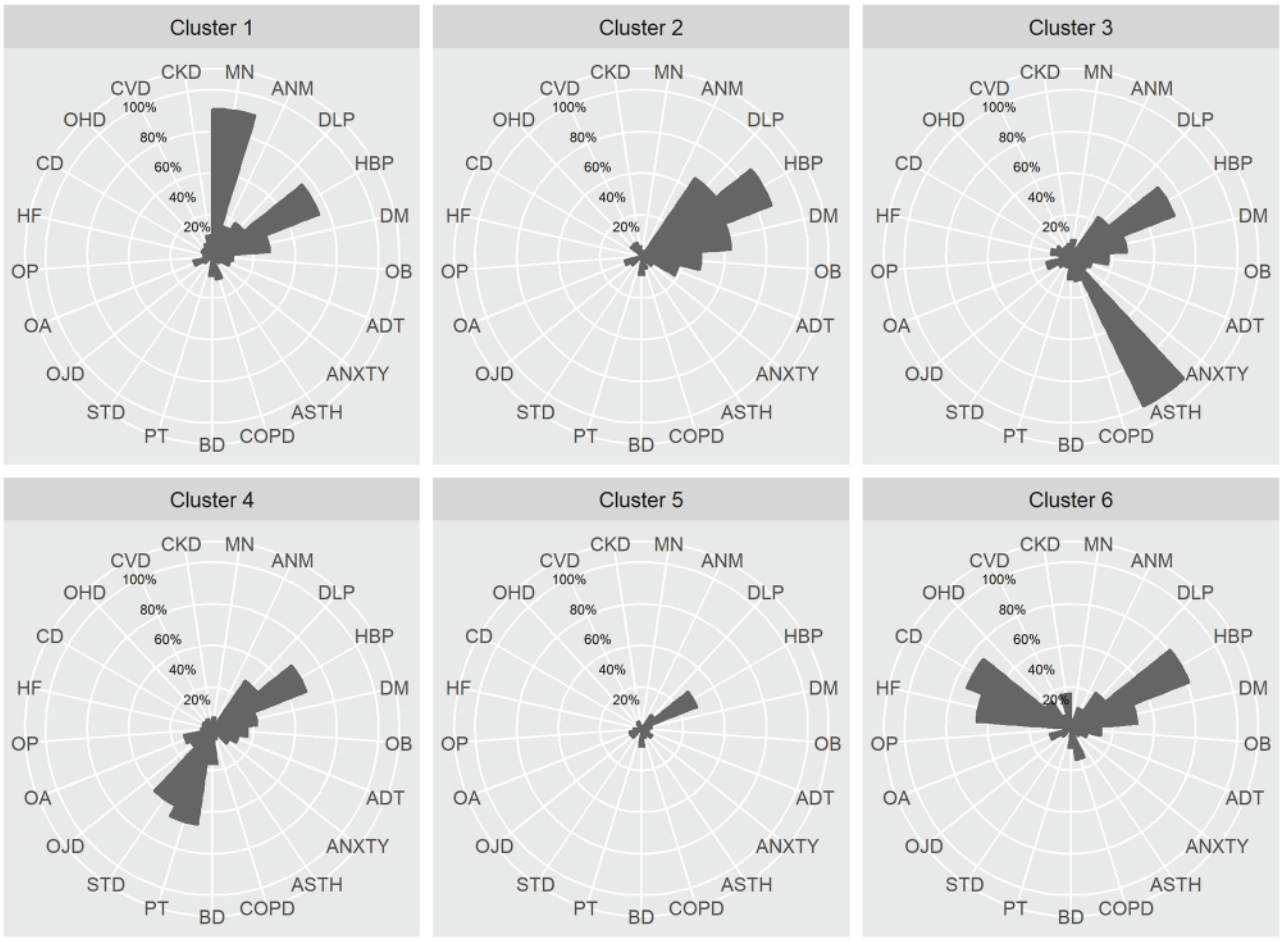

Fig 2. The proportion of each comorbidity in each cluster. Cluster 1: Neoplastic patients. Cluster 2: Metabolic syndrome patients. Cluster 3: Asthmatic patients. Cluster 4: Musculoskeletal and joint disorders patients. Cluster 5: Patients with few comorbidities. Cluster 6: Oldest and cardiac disease patients. Abbreviations: DLP, dyslipidaemia; OB, obesity; BD, back disorders; OA, osteoarthrosis; HF, heart failure; CD, cardiac dysrhythmia; ADT, addiction; ANXTY, anxiety; OHD, other heart disease; OJD, other joint disease; PT, peripheral tendinitis; CKD, chronic kidney disease; ASTH, asthma; STD, soft tissue disease; MN, malignant neoplasm; HBP, hypertension; CVD, cerebrovascular; COPD, chronic obstructive pulmonary disease; ANM, anaemia; DM, diabetes mellitus; OP, osteoporosis.

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included 7,234 patients (10.3%), who had peripheral tendinitis (58.2%), joint diseases (15.2%) and muscular disease (51.0%); this group had the lowest mortality rate (1.4%). Cluster 5 (Patients with few comorbidities) grouped the patients with few comorbidities (n = 25,088 patients, 35.6%). Use of healthcare resources by this group was low, as was the mortality rate (3.6%). Cluster 6 (Oldest and cardiac disease patients, n = 7,190, 10.2%) had a median age of 72.0 years [IQR 64.5;79.5], and patients had dysrhythmia (67.5%) and heart failure (57.1%). This group had one of the highest mortality rates (14.6%).

Mortality rates in both Cluster 1 and 6 were high, but the patient groups differed with respect to the primary comorbidity diagnosis and healthcare resource use. Specifically, patients in Cluster 6 used a wide range of healthcare resources whereas those in Cluster 1 had more hospital and nursing home visits (Fig 3). Mortality rates in Cluster 2 and 4 were also had similar (low), but patients in Cluster 4 used more primary care resources than those in Cluster 2. In addition, mortality rates were similar in Clusters 3 and 5, but healthcare resource use was again different, being very low for Cluster 5 and higher for Cluster 3.

Table 2. Patient demographic characteristics and annual proportion of health care resource use for the entire cohort and by cluster.

	All clusters	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6	p value
	N = 70,469	N = 7,340	N = 19,535	N = 4,082	N = 7,234	N = 25,088	N = 7,190	
Gender (male)	52805 (74.9%)	5742 (78.2%)	15285 (78.2%)	1917 (47.0%)	4617 (63.8%)	20139 (80.3%)	5105 (71.0%)	<0.001
Age (years)	64.5 [57.0;72.0]	69.5 [62.0;77.0]	64.5 [57.0;69.5]	67.0 [57.0;74.5]	62.0 [57.0;69.5]	62.0 [52.0;67.0]	72.0 [64.5;79.5]	<0.001
CPAP time (months)	34.9 [14.8;58.5]	38.5 [17.9;63.6]	36.8 [15.4;60.8]	32.8 [12.8;55.5]	33.5 [13.7;57.2]	34.2 [14.8;57.4]	32.1 [13.3;56.6]	<0.001
Mortality	3726 (5.29%)	1103 (15.0%)	364 (1.86%)	198 (4.85%)	102 (1.41%)	906 (3.61%)	1053 (14.6%)	<0.001
Nurse home (0 visits)	69084 (98.0%)	6974 (95.0%)	19368 (99.1%)	3949 (96.7%)	7161 (99.0%)	24882 (99.2%)	6750 (93.9%)	<0.001
Nurse home (>0 visits)	1385 (1.97%)	366 (4.99%)	167 (0.85%)	133 (3.26%)	73 (1.01%)	206 (0.82%)	440 (6.12%)	
Hospital (0 visits)	46183 (65.5%)	3335 (45.4%)	14144 (72.4%)	2362 (57.9%)	4768 (65.9%)	18722 (74.6%)	2852 (39.7%)	<0.001
Hospital (1 visit)	13510 (19.2%)	1812 (24.7%)	3407 (17.4%)	841 (20.6%)	1560 (21.6%)	4231 (16.9%)	1659 (23.1%)	
Hospital (>1 visit)	10776 (15.3%)	2193 (29.9%)	1984 (10.2%)	879 (21.5%)	906 (12.5%)	2135 (8.51%)	2679 (37.3%)	
Primary care (0–2.5 visits)	19382 (27.5%)	1410 (19.2%)	3782 (19.4%)	667 (16.3%)	920 (12.7%)	11896 (47.4%)	707 (9.83%)	<0.001
Primary care (2.5–5 visits)	17660 (25.1%)	1721 (23.4%)	5703 (29.2%)	882 (21.6%)	1735 (24.0%)	6679 (26.6%)	940 (13.1%)	
Primary care (>5 visits)	33427 (47.4%)	4209 (57.3%)	10050 (51.4%)	2533 (62.1%)	4579 (63.3%)	6513 (26.0%)	5543 (77.1%)	
Pharmacy (0–1.5 drugs)	24893 (35.3%)	1916 (26.1%)	5251 (26.9%)	916 (22.4%)	2004 (27.7%)	13873 (55.3%)	933 (13.0%)	<0.001
Pharmacy (1.5–3.5 drugs)	22919 (32.5%)	2264 (30.8%)	7879 (40.3%)	1148 (28.1%)	2620 (36.2%)	7336 (29.2%)	1672 (23.3%)	
Pharmacy (>3.5 drugs)	22657 (32.2%)	3160 (43.1%)	6405 (32.8%)	2018 (49.4%)	2610 (36.1%)	3879 (15.5%)	4585 (63.8%)	

Data are presented as median [interquartile range; IQR] and n (%).

Cluster 1: Neoplastic patients. Cluster 2: Metabolic syndrome patients. Cluster 3: Asthmatic patients. Cluster 4: Musculoskeletal and joint disorders patients. Cluster 5: Patients with few-comorbidities. Cluster 6: Oldest and cardiac disease patients.

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Discussion

This study is the first cluster analysis involving the entire CPAP-treated population with OSA of Catalonia. Using data from the Catalan Health System, we defined a general profile of OSA patients treated with CPAP, largely characterised by middle-aged men, with a high prevalence of hypertension, dyslipidaemia, diabetes and obesity. At the same time, cluster analysis identified six patient groups that showed different patterns of comorbidities, mortality, and health-care resource use.

Similar to previous literature, we found that hypertension, diabetes and dyslipidaemia were highly prevalent among OSA patients [12–15]. In a sample of more than 18,000 patients from a prospective national registry, Bailey et al. also confirmed the high burden of comorbidities in OSA patients, identifying six clusters [8]. However, similar to other previous cluster studies, they characterised OSA patients using data from a national registry, clinical practice and sleep registry analysis [8–11], while we exclusively used the coded diseases and discharge data from hospitals, nursing homes and primary care institutions, the number of visits to the emergency room or primary care, and medication use. The observation of a cluster comprised entirely of patients with asthma, mostly women, confirmed previous observations of an OSA-asthma overlap syndrome [16] and suggests a need for more specific studies in this field. Asthma is, in fact, a recognised risk factor for developing OSA [17] and women with OSA are more likely to be diagnosed with asthma [18].

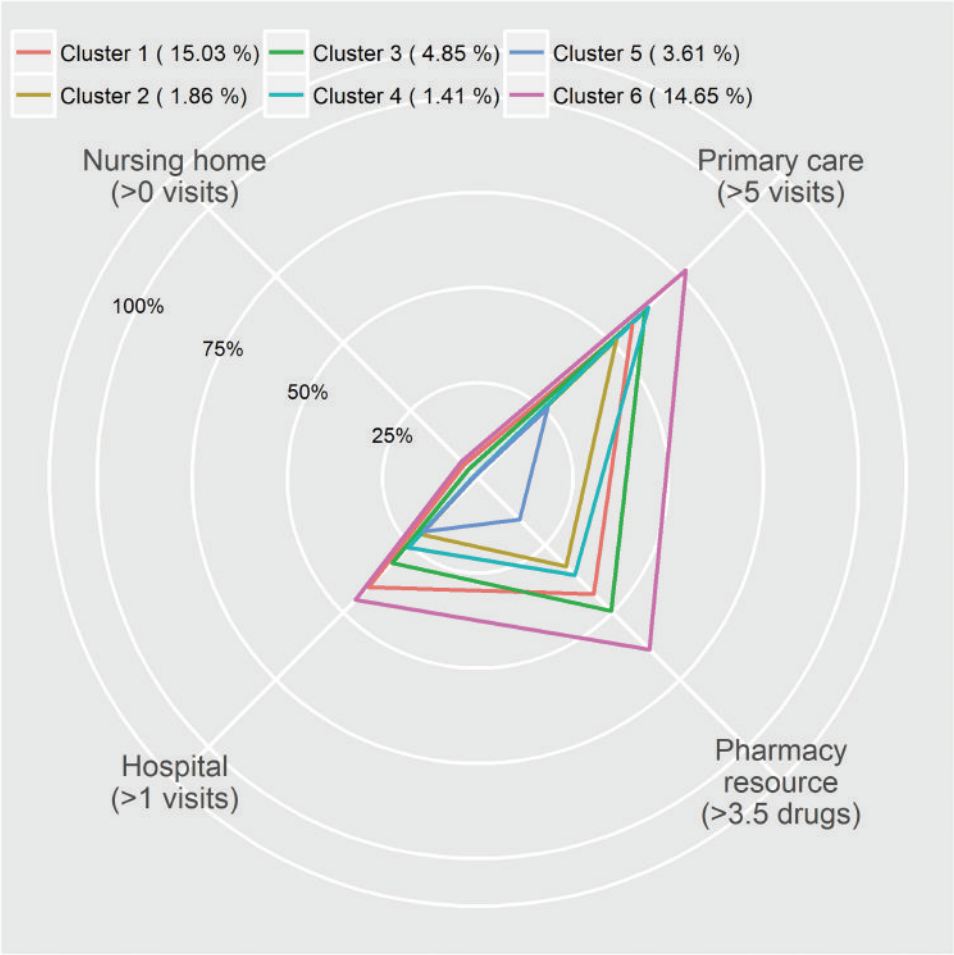

Fig 3. Percentages of high use of health care resources per year in each cluster. Cluster 1: Neoplastic patients. Cluster 2: Metabolic syndrome patients. Cluster 3: Asthmatic patients. Cluster 4: Musculoskeletal and joint disorders patients. Cluster 5: Patients with few comorbidities. Cluster 6: Oldest and cardiac disease patients. (% Mortality).

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Over and above the characterisation of six clusters, the CPAP-treated population from Catalonia could be divided into two major groups. Almost 20% of the overall population were allocated to clusters 1 and 6, and showed the most advanced age and the highest mortality. The majority of patients (88.5%) in Cluster 1 (Neoplastic patients) had a malignant neoplasm, most frequently of genitourinary or gastrointestinal origin. This is of interest given some current literature reports of a higher prevalence of cancer (particularly pancreatic or renal tumours) in patients with OSA [19]. Cluster 6 (Oldest and cardiac patients) included the oldest individuals (median age 72.0 years), with the highest prevalence of cardiac failure and cardiac arrhythmias. Patients in Clusters 1 and 6 showed the highest mortality and rate of hospitalisation, almost certainly due to the underlying comorbidities rather than as a result of OSA. The presence of cardiovascular diseases has been associated with a worse prognosis in patients using CPAP [20] and CPAP treatment of sleep apnoea has not been shown to improve survival in patients with these comorbidities [21]. Furthermore, in patients over 65 years of age, the presence of OSA seems to have only a slight impact on quality of life, which is determined to a greater extent by the presence of comorbidities [22]. In contrast, more than a half of our population was male,

had few comorbidities, and low mortality and healthcare resource use (Clusters 2 and 5). In these groups, OSA appears to be the most important determinant of patient prognosis [23], and patients with these characteristics could be more likely to benefit from CPAP treatment.

Given the different phenotypes identified, the results of our study could have an important impact on Catalan health policies. The Catalan Health System provides free healthcare services to more than 7 million people [24] with annual spending of around €8,000 million [25]. CPAP treatment is provided at no cost to approximately 70,000 people, and cost effectiveness is only achieved after the second year of treatment and exclusively in patients who are compliance with therapy [26]. In Catalonia CPAP therapy is typically prescribed to patients with severe OSA or for more mild disease that is accompanied by daytime hypersomnolence or other symptoms attributable to OSA. Daily CPAP compliance is closely monitored because CPAP treatment is completely free of charge only for patients who used their device for more than 3 hours per night; if this is not the case, CPAP is withdrawn [27]. Even in the absence of specific data about the compliance of our population, it would be reasonable to assume device usage of at least 3 h/night given the treatment criteria and the fact that median duration of CPAP use was 34 months.

Understanding inter-patient differences in clinical presentations of OSA could facilitate more efficient resource management and provision of care. In the light of cluster analysis results, one-third of all CPAP-treated OSA patients in Catalonia (Clusters 1 & 6) are in fact receiving a treatment that probably will not markedly influence their life expectancy or quality of life. Medical resources could be better spent for the remaining population of patients with few comorbidities, for whom a clinical benefit of CPAP treatment would be expected.

This study has several strengths, including the large and comprehensive study population and the statistical method used. In addition, data about patient characteristics, comorbidities and resource use were provided by AQuAS, ensuring high quality information. Furthermore, data were collected from different public health settings (primary care, nursing homes and hospitals) increasing the generalisability of our findings. However, there are some limitations to be considered. Firstly, the absence of clinical information about the study population (e.g. symptoms, quality of life, sleep records, CPAP compliance) limits the ability to fully characterise each cluster. Secondly, use of the ICD-9 classification system reduces the specificity of disease definitions. The ICD-9 sometimes groups similar diseases together, reducing the ability to differentiate between them. However, it does ensure the homogeneity and accuracy of the disease classification. Finally, the absence of a control group also limits our capacity to define clusters and assess whether the features identified are specific to OSA patients.

Conclusions

This study used cluster analysis based on diagnostic profile to characterise the entire CPAP-treated population of Catalonia for the first time. Six clusters were identified, but the majority of patients could be distributed into two broad groups: one older with high mortality and healthcare resource use, and the other with few comorbidities, low mortality and lower healthcare resource use. Our study highlights the heterogeneity of OSA patients on CPAP treatment, emphasises the importance of identifying the indication and expected benefits of CPAP in specific OSA phenotypes, and offers the opportunity to tailor interventions for specific patient groups.

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References

1. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol. 2013; 177: 1006–14. https://doi.org/10.1093/aje/kws342 PMID: 23589584
2. Campos-Rodriguez F, Martinez-Garcia MA, Martinez M, Duran-Cantolla J, Peña Mde L, Masdeu MJ, et al. Spanish Sleep Network. Association between obstructive sleep apnea and cancer incidence in a large multicenter Spanish cohort. Am JRespirCritCare Med. 2013; 187;99–105.
3. Sánchez-de-la-Torre M, Campos-Rodriguez F, Barbé F. Obstructive sleep apnoea and cardiovascular disease. Lancet Respir Med. 2013; 1:61–72. https://doi.org/10.1016/S2213-2600(12)70051-6 PMID: 24321805
4. Terán-Santos J, Jiménez-Gómez A, Cordero-Guevara J. The association between sleep apnea and the risk of traffic accidents. Cooperative Group Burgos-Santander. N Engl J Med. 1999; 340:847–851. https://doi.org/10.1056/NEJM199903183401104 PMID: 10080847
5. Barbé F, Pericás J, Muñoz A, Findley L, Antó JM, Agustí AG. Automobile accidents in patients with sleep apnea syndrome. An epidemiological and mechanistic study. Am J Respir Crit Care Med. 1998; 158:18–22. https://doi.org/10.1164/ajrccm.158.1.9709135 PMID: 9655701

6. Barbé F, Durán-Cantolla J, Sánchez-de-la-Torre M, Martínez-Alonso M, Carmona C, Barceló A, et al. Spanish Sleep And Breathing Network. Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in non sleepy patients with obstructive sleep apnea: a randomized controlled trial. JAMA 2012; 307:2161–8. https://doi.org/10.1001/jama.2012.4366 PMID: 22618923
7. Martínez-García MA, Capote F, Campos-Rodríguez F, Lloberes P, Díaz de Atauri MJ, Somoza M, et al. Spanish Sleep Network. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: the HIPARCO randomized clinical trial. JAMA. 2013; 310:2407–15. https://doi.org/10.1001/jama.2013.281250 PMID: 24327037
8. Bailly S, Destors M, Grillet Y, Richard P, Stach B, Vivodtzev I, et al. Obstructive sleep apnea: acluster analysis at time ofdiagnosis. PLoS One. 2016; 11(6):e0157318. https://doi.org/10.1371/journal.pone.0157318 PMID: 27314230
9. Howell S, Coory M, Martin J, Duckett S.Using routine inpatient data to identify patients at risk of hospital readmission. BMC Health Serv Res 2009; 9:96. https://doi.org/10.1186/1472-6963-9-96 PMID: 19505342
10. Ye L, Pien GW, Ratcliffe SJ, Björnsdottir E, Arnardottir ES, Pack AI, et al. The different clinical faces of obstructive sleep apnoea: a cluster analysis. Eur Respir J. 2014; 44:1600–7. https://doi.org/10.1183/09031936.00032314 PMID: 25186268
11. Lacedonia D, Carpagnano GE, Sabato R, Storto MM, Palmiotti GA, Capozzi V, et al. Characterization of obstructive sleep apnea-hypopnea sydrome (OSA) population by means of cluster analysis. J Sleep Res. 2016; 25:724–30. https://doi.org/10.1111/jsr.12429 PMID: 27191534
12. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. J Am Coll Cardiol. 2008; 52:686–717. https://doi.org/10.1016/j.jacc.2008.05.002 PMID: 18702977
13. Kent BD, McNicholas WT, Ryan S. Insulin resistance, glucose intolerance and diabetes mellitus in obstructive sleep apnoea. J Thorac Dis. 2015; 7:1343–57. https://doi.org/10.3978/j.issn.2072-1439.2015.08.11 PMID: 26380761
14. Trzepizur W, Le Vaillant M, Meslier N, Masson P, Humeau MP, et al. Independent association between nocturnal intermittent hypoxemia and metabolic dyslipidemia. Chest. 2013; 143:1584–9. https://doi.org/10.1378/chest.12-1652 PMID: 23699812
15. Pamidi S, Tasali E. Obstructive sleep apnea and type 2 diabetes: is there a link? Front Neurol. 2012; 3:126. https://doi.org/10.3389/fneur.2012.00126 PMID: 23015803
16. Madama D, Silva A, Matos MJ. Overlap syndrome- asthma and obstructive sleep apnea. Rev Port Pneumol. 2016; 22:6–10. https://doi.org/10.1016/j.rppnen.2015.08.005 PMID: 26603307
17. Teodorescu M, Barnet JH, Hagen EW, Palta M, Young TB, Peppard PE. Association between asthma and risk of developing obstructive sleep apnea. JAMA. 2015; 313:156–64. https://doi.org/10.1001/jama.2014.17822 PMID: 25585327
18. Greenberg-Dotan S, Reuveni H, Simon-Tuval T, Oksenberg A,Tarasiuk A. Gender differences in morbidity and health care utilization among adult obstructive sleep apnea patients. Sleep. 2007; 30:1173–80. PMID: 17910389
19. Gozal D, Ham SA, Mokhlesi B. Sleep apnea and cancer: Analysis of a nationwide population sample. Sleep. 2016; 39:1493–500. https://doi.org/10.5665/sleep.6004 PMID: 27166241
20. Jennum P, Tønnesen P, Ibsen R, Kjellberg Jm. Obstructive sleep apnea: effect of comorbidities and positive airway pressure on all-cause mortality. Sleep Med. 2017 Aug; 36:62–66. https://doi.org/10.1016/j.sleep.2017.04.018 PMID: 28735924
21. McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, Mediano O, et al. CPAP for prevention of cardiovascular events in obstructive sleep apnea. N Engl J Med. 2016; 375:919–31. https://doi.org/10.1056/NEJMoa1606599 PMID: 27571048
22. Martınez-Garcia MA, Soler-Cataluña JJ, Roman-Sanchez P, Gonzalez V, Amoros C, Montserrat JM. Obstructive sleep apnea has little impact on quality of life in the elderly. Sleep Med. 2009 Jan; 10(1):104–11 https://doi.org/10.1016/j.sleep.2007.11.009 PMID: 18207454
23. Gottlieb DJ, Yenokyan G, Newman AB, O'Connor GT, Punjabi NM, et al. A prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the Sleep Heart Health study. Circulation. 2010; 122: 352–60. https://doi.org/10.1161/CIRCULATIONAHA.109.901801 PMID: 20625114
24. Generalitat de Catalunya. Institut d'Estadistica de Catalunya. http://www.idescat.cat/pub/?id=aec&n=245&lang=es Date last accessed: March 28 2017.

25. Generalitat de Catalunya. Institut d'Estadistica de Catalunya. http://www.idescat.cat/pub/?id=aec&n=535&lang=es Date last accessed: March 28 2017.

26. Català R, Villoro R, Merino M, Sangenís S, Colomés L, Hernández Flix S, Pérez de Llanod LA. Cost-effectiveness of Continuous Positive Airway Pressure Treatmentin Moderate-Severe Obstructive Sleep Apnea Syndrome. Arch Bronconeumol. 2016; 52(9):461–469. https://doi.org/10.1016/j.arbres.2016.02.005 PMID: 26993090

27. http://aquas.gencat.cat/web/.content/minisite/aquas/projectes/atles/atles_variacions/Pressio_positiva_continua_respiratories/PressioPositivaContinua_CPAP_Atles_Variacions_AQuAS.pdf

5.3 ARTICLE 3

"Management of continuous positive airway pressure treatment compliance using telemonitoring in obstructive sleep apnoea "

Cecilia Turino, Jordi de Batlle, Holger Woehrle, Ana Mayoral, Anabel Lourdes Castro-Grattoni , Sílvia Gómez, Mireia Dalmases, Manuel Sánchez-de-la-Torre and Ferran Barbé

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Management of continuous positive airway pressure treatment compliance using telemonitoring in obstructive sleep apnoea

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Telemonitoring did not improve CPAP compliance, showed lower patient satisfaction, but proved to be cost-effective http://ow.ly/UvHX306AC0V

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ABSTRACT Continuous positive airway pressure (CPAP) is an effective treatment for obstructive sleep apnoea (OSA), but treatment compliance is often unsatisfactory. This study investigated the efficacy and cost-effectiveness of telemonitoring for improving CPAP compliance.

100 newly diagnosed OSA patients requiring CPAP (apnoea–hypopnoea index >15 events·h^{-1}) were randomised to standard management or a telemonitoring programme that collected daily information about compliance, air leaks and residual respiratory events, and initiated patient contact to resolve issues. Clinical/anthropometric variables, daytime sleepiness and quality of life were recorded at baseline and after 3 months. Patient satisfaction, additional visits/calls, side-effects and total costs were assessed.

There were no significant differences between the standard and telemedicine groups in terms of CPAP compliance (4.9±2.2 *versus* 5.1±2.1 h·night^{-1}), symptoms, clinical variables, quality of life and unwanted effects. Telemedicine was less expensive than standard management (EUR123.65 *versus* EUR170.97; p=0.022) and was cost-effective (incremental cost-effectiveness ratio EUR17 358.65 per quality-adjusted life-year gained). Overall patient satisfaction was high, but significantly more patients rated satisfaction as high/very high in the standard management *versus* telemedicine group (96% *versus* 74%; p=0.034).

Telemonitoring did not improve CPAP treatment compliance and was associated with lower patient satisfaction. However, it was more cost-effective than traditional follow-up.

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Introduction

Obstructive sleep apnoea (OSA) is a highly prevalent disorder, affecting 10% of adult men and 4% of adult women in Western countries [1]. It is characterised by recurrent collapse of the upper airway during sleep, leading to nocturnal hypoxaemia, sleep fragmentation and daytime hypersomnolence. Untreated OSA is associated with a higher risk of developing arterial hypertension, cardiovascular and cerebrovascular diseases, as well as a worse quality of life (QoL) [2–5]. Moreover, OSA is a risk factor for traffic accidents and has an important socioeconomic impact [6, 7].

First-line therapy for moderate to severe OSA is the application of continuous positive airway pressure (CPAP), which provides a pneumatic splint and prevents upper airway collapse during sleep [8]. Good CPAP adherence (use of the device for at least 4 $h \cdot night^{-1}$) [9], may improve QoL and daytime sleepiness, decrease the risk of new-onset hypertension and cardiovascular events, and reduce blood pressure in patients with resistant hypertension [10–13]. Adherence is therefore essential for the efficacy of CPAP treatment, and the optimisation of adherence and compliance is an important aspect of patient management.

Although published evidence shows that CPAP is a highly effective therapy, a significant proportion of patients (up to 36%) underuse or even discontinue CPAP [14–16], mostly because of treatment-related side-effects (*e.g.* pressure intolerance, claustrophobia, mask displacement and machine noise) [17] and lack of improvement in symptoms. Many of these problems could be solved by a closer follow-up, allowing patients to continue effective therapy, but this would increase the workload for sleep units that are already operating at full capacity and increase the cost of managing OSA. Therefore, new methods of facilitating and improving CPAP compliance are needed, particularly during the first months of treatment when long-term CPAP compliance is established [18].

Recent technologies have already enabled CPAP devices to monitor applied pressures, air leaks, the apnoea–hypopnoea index (AHI) and objective adherence, and to send this information to a patient's healthcare provider on a daily basis. These systems could allow early detection of problems and facilitate appropriate interventions, thereby improving early experience with CPAP and potentially improving long-term adherence [19].

This pilot study compared the effectiveness of a telemonitoring-based strategy *versus* standard follow-up on compliance with CPAP treatment in OSA patients.

Methods

Study design and patients

This prospective randomised controlled study was conducted at the sleep unit of St Maria Hospital (Lleida, Spain) between January and July 2015, and included adult patients (>18 years) with newly diagnosed OSA requiring treatment with CPAP (AHI >15 $events \cdot h^{-1}$). Assuming an α risk of 0.05 and a β risk of 0.2 in a two-sided test, a sample size of 49 subjects in each group was needed to detect differences $\geqslant$1 h in CPAP treatment compliance. A common standard deviation of 1.75 was assumed. Given the high motivation of both professionals and patients to be involved, no dropouts were anticipated and thus a total of 100 patients were planned to be recruited.

Patients were randomised to have CPAP therapy managed using standard care or a telemonitoring-based strategy and followed up over 3 months. Patients with impaired lung function (overlap syndrome, obesity hypoventilation and restrictive disorders), severe heart failure, psychiatric disorders, periodic leg movements, pregnancy, other dysomnias or parasomnias, and/or a history of previous CPAP treatment were excluded. The study was approved by the hospital's ethics committee and registered at ClinicalTrials.gov (trial number NCT02517346). All recruited patients signed an informed consent form.

Interventions

Patients randomised to standard care were fitted with a mask and given a CPAP device (AirSense 10; ResMed, Martinsried, Germany) and a leaflet explaining how to use it. A short instruction session on how to use a CPAP device was also given to patients and partners in the sleep unit by a trained nurse with experience in the follow-up of CPAP-treated patients. This included a practical demonstration of how to put on the mask, and the correct management and cleaning of the tubes, masks and humidifier. Information on how to turn the CPAP device on and off was provided by the homecare provider at the time of machine delivery. All patients were visited after 1 month of treatment by the specialist nurse at the sleep unit. Information about CPAP pressure, compliance and adherence (use of CPAP for $\geqslant$4 $h \cdot day^{-1}$), residual respiratory events and leaks were downloaded from the device. CPAP-related side-effects, CPAP machine care and maintenance (changes of mask, tubes and humidifier), and the number of additional visits and calls were recorded by the nurse.

In the telemonitoring group, patients were also fitted with a mask and given a CPAP device (AirSense 10) and a leaflet explaining how to use it, and received the same training sessions from the same personnel as

in the standard care arm. Each CPAP device given to patients in this group was equipped with mobile 2G (GSM/GPRS) technology capable of sending daily information on CPAP adherence, CPAP pressures, mask leak and residual respiratory events to the MyOSA–Oxigen Salud web database (www.oxigensalud.com) Automatic alarms for the provider were generated in case of mask leak >30 $L \cdot min^{-1}$ for >30% of the night or usage of <4 $h \cdot night^{-1}$ on two consecutive nights. In case of alarm, the pulmonary specialist medical officer of the CPAP provider contacted the patient, providing case-by-case problem solving. This included suggestions about how to minimise symptoms (dry mouth, mask issues, discomfort with the device), specific interventions to improve compliance (mask changing, chin strap, pressure or humidifier settings, saline nasal sprays) and support for the patient in the use of CPAP.

Assessments

Clinical variables and anthropometric parameters (age, sex, blood pressure, body weight, height, body mass index (BMI), neck, waist and hip circumference), daytime sleepiness (based on Epworth Sleepiness Scale score) and QoL (assessed using the EuroQol EQ-5D health questionnaire; www.euroqol.org) were recorded by a sleep unit physician during clinic visits at baseline and at 3 months. At the 3-month evaluation, patients were asked to rate their satisfaction with therapy using a questionnaire, and information about CPAP pressures, compliance and adherence (CPAP utilisation $\geqslant$4 $h \cdot day^{-1}$), residual respiratory events, and leaks was downloaded from all CPAP devices by the physician. In addition, the physician recorded CPAP-related side-effects, CPAP machine care and maintenance (changes of mask, tubes and humidifier), and the number of additional visits and calls.

Costs

Total direct and indirect costs of each intervention were assessed to perform cost and cost-effective analyses. The costs of hospital visits and telephone consultations with sleep unit physicians were assessed using prices provided by the Catalan Institute of Health [20]. No OSA-related hospital admissions were recorded during the follow-up and thus no additional costs due to hospitalisations had to be added. Costs for telephone consultations with the CPAP provider, visits from the CPAP provider, changes in materials related to the CPAP device, and additional costs for 2G (GSM/GPRS) daily data transfer and patients' activation and maintenance of daily data monitoring by the CPAP provider in the telemonitoring group were assessed using prices provided by the CPAP provider. All costs related to the CPAP provider were paid by the Catalan Institute of Health and thus all direct costs were assessed from a healthcare system perspective. Patients' costs related to travel to the sleep unit or CPAP provider offices were calculated and included as indirect costs, and thus these indirect costs were assessed from a patient perspective. A full list of costs recorded is provided in online supplementary table S1. The cost-effectiveness of both strategies for managing OSA patients undergoing CPAP treatment was evaluated by calculating the incremental cost-effectiveness ratio (ICER) [21]. The ICER is based on total costs incurred and quality-adjusted life-years (QALYs) gained, and calculates the ratio between the differences in the cost (EUR) and effectiveness (QALYs) of both strategies.

Statistical analysis

Continuous variables were expressed as mean±standard deviation, while categorical variables were reported as absolute numbers and percentages. Differences between study groups were assessed using the Chi-squared or Fisher's exact test to compare dichotomous variables, and the t-test for continuous variables. Linear or logistic regression analyses were used, as appropriate, to compare differences between study groups. Age, sex, AHI and variables that differed at baseline ($p<0.100$) were included as covariates. Cost differences between study groups were assessed using the Mann–Whitney two-sample statistic. Sensitivity analyses were performed for 25% and 50% increases in CPAP provider costs.

All tests were two-sided and p-values <0.05 were considered statistically significant. All analyses were performed on both an intention-to-treat and a per-protocol basis. Statistical analyses were performed using Stata version 12.1 (StataCorp, College Station, TX, USA).

Results

A total of 100 subjects were randomised: 48 to standard care and 52 to telemedicine. Baseline patient demographic and clinical characteristics in the two intervention groups are shown in table 1. Overall, patients had a mean age of 55 years, 23% were women, were mostly obese (mean BMI 35 $kg \cdot m^{-2}$) and had a high AHI (mean 52 $events \cdot h^{-1}$). The only significant differences between the standard and telemedicine groups at baseline were a lower waist/hip ratio and a higher incidence of dyslipidaemia in the telemedicine *versus* standard care group (table 1). All results presented are for the intention-to-treat analysis; similar results were obtained in the per-protocol analysis.

TABLE 1 Baseline patient demographic and clinical characteristics in 100 study patients

	Standard care	Telemedicine	p-value#
Subjects	48	52	
Female	11 (23)	12 (23)	0.985
Age years	54±12	56±13	0.292
Weight kg	97±19	99±21	0.582
Height m	1.67±0.10	1.67±0.11	0.891
BMI kg·m^{-2}	35±7	35±7	0.853
Neck circumference cm	43±4	42±4	0.308
Waist circumference cm	111±14	112±15	0.638
Hip circumference cm	110±12	115±14	0.066
Waist/hip ratio	1.01±0.08	0.98±0.10	0.110
Smoking			0.102
Never	16 (33)	27 (54)	
Former	15 (31)	9 (18)	
Current	17 (35)	14 (28)	
Alcohol intake >2 drinks·week^{-1}	18 (38)	17 (35)	0.771
AHI events·h^{-1}	53±26	52±25	0.726
Total apnoea index events·h^{-1}	34±27	35±26	0.868
Obstructive apnoea index events·h^{-1}	31±25	33±24	0.718
Mean $Sa0_2$ %	91±4	91±3	0.832
Minimum $Sa0_2$ %	73±10	73±10	0.805
Time with $Sa0_2$ <90% %	21±23	21±21	0.907
Awake $Sa0_2$ %	98±1	97±2	0.216
Epworth Sleepiness Scale score	10±4	9±5	0.188
Systolic arterial blood pressure mmHg	134±19	136±15	0.691
Diastolic arterial blood pressure mmHg	89±14	89±13	0.927
Comorbidities			
Depression	10 (21)	9 (18)	0.723
Anxiety	8 (17)	9 (18)	0.899
Hypertension	23 (48)	28 (57)	0.363
Cardiopathy	9 (19)	12 (24)	0.493
Neurological disease	4 (8)	6 (12)	0.549
Respiratory disease	10 (21)	5 (10)	0.136
Diabetes	9 (19)	6 (12)	0.354
Dyslipidaemia	14 (29)	27 (55)	0.010
Obesity	32 (67)	29 (58)	0.376
Neoplasia	1 (2)	4 (8)	0.176
Nasal obstruction	22 (46)	19 (40)	0.536

Data are presented as n, n (%) or mean±SD, unless otherwise stated. Numbers of subjects may vary slightly in each row due to missing values. BMI: body mass index; AHI: apnoea–hypopnoea index; $Sa0_2$: arterial oxygen saturation. #: p-values evaluating the differences between groups, using the t-test, Chi-squared test or Fisher's exact test as appropriate.

There were no significant differences between the standard care and telemedicine groups with regard to compliance with CPAP, improvement in symptoms and QoL, changes in clinical variables, and treatment-related side-effects after 3 months of follow-up (table 2).

Overall patient satisfaction at 3 months was good (table 3). Patients managed using telemedicine reported significantly lower overall satisfaction than those receiving standard care and tended to be less satisfied about appropriate contact with the hospital (table 3). Overall, patients managed using telemedicine placed a positive value on all aspects of the telemonitoring programme, with the exception of privacy aspects (table 3).

Values for direct and indirect costs assessed during the study are summarised in table 4. The total average cost per randomised patient was 28% lower in the telemonitoring group than in the standard care group. This was primarily a result of lower costs for planned follow-up visits to the sleep unit, which are not required when telemonitoring is used. The number of QALYs gained was similar in each treatment group (0.060 for standard care and 0.057 for telemonitoring). The ICER for the telemonitoring strategy compared with standard care was EUR17 358.65 per QALY gained. Sensitivity analyses showed that increasing CPAP provider costs by 25% was associated with savings of EUR39.88 for telemonitoring *versus* standard care (p=0.048 for between-group comparison) and with savings of EUR32.43 when CPAP provider costs were increased by 50% (p=0.116) (online supplementary table S2).

TABLE 2 Continuous positive airway pressure treatment compliance, symptoms, clinical variables, quality of life and treatment-related side-effects at 3 months of follow-up

	Standard care	Telemedicine	p-value	
			Unadjusted[#]	Adjusted[¶]
Subjects	48	52		
Treatment compliance h·night^{-1}				
At 1 month	5.2±2.1	4.8±2.3	0.415	0.711
At 3 months	4.9±2.2	5.1±2.1	0.709	0.627
Symptom improvement				
Snoring	47 (100)	43 (94)		
Witnessed apnoeas	34 (79)	36 (86)	0.571	0.375
Nocturia	28 (60)	28 (60)	1.000	0.725
Daytime sleepiness	28 (58)	27 (59)	1.000	0.506
Night-time asphyxia	20 (42)	20 (44)	1.000	0.846
Night-time awakenings	23 (48)	22 (47)	1.000	0.536
Restless legs	6 (13)	5 (10)	0.759	0.594
Change from baseline in clinical variables				
Systolic arterial pressure mmHg	−3.1±18.0	−4.3±14.8	0.710	0.643
Diastolic arterial pressure mmHg	−5.3±10.6	−5.9±11.6	0.805	0.923
BMI kg·m^{-2}	−0.31±1.5	−0.28±1.6	0.930	0.535
Quality of life				
EQ-5D score at baseline	0.767±0.23	0.783±0.19	0.703	0.548
EQ-5D score at 3 months	0.827±0.21	0.840±0.18	0.730	0.309
EQ-5D score change[+]	0.060±0.17	0.057±0.19	0.941	0.700
Improvement in EQ-5D score	10 (21)	10 (20)	1.000	0.532
Side-effects				
Secondary effects[§]	18 (38)	23 (46)	0.420	0.219
Treatment complications[f]	4 (8)	3 (6)	0.715	0.930

Data are presented as n, mean±SD or n (%), unless otherwise stated. Numbers of subjects may vary slightly in each row due to missing values. BMI: body mass index. [#]: unadjusted p-values determined using the t-test or Fisher's exact test as appropriate; [¶]: adjusted p-values based on linear or logistic regression models adjusted for age, sex, apnoea–hypopnoea index, Epworth Sleepiness Scale score, dyslipidaemia, waist/hip ratio and nocturnal motor activity; [+]: EQ-5D score at 3 months minus EQ-5D score at baseline; [§]: secondary effects included allergy to components of the device, headache, facial pain and bruises; [f]: treatment complications included aerophagia and mouth and/or nose dryness.

Discussion

This study is the second randomised controlled clinical trial to assess the effectiveness of telemonitoring for improving CPAP compliance, the largest to date in terms of the number of enrolled patients, and the first to include cost and cost-effectiveness analyses. Although there were no significant overall differences in CPAP treatment compliance between OSA patients managed using telemonitoring compared with standard care, use of the telemonitoring strategy reduced overall costs and was cost-effective. However, patient satisfaction was higher in the standard care group.

Contrary to expectations, telemonitoring did not improve CPAP compliance after 3 months of follow-up in our study. This is in contrast to the results of a Canadian randomised controlled trial enrolling 75 patients that showed a better compliance with auto-titrating positive airway pressure after 3 months of management using telemonitoring compared with standard care (191±147 *versus* 105±118 min·day^{-1}; p=0.006) [19]. These contrasting results could be explained by differences between the studies in terms of compliance in control patients. In the present study, patients managed using standard care had a mean CPAP usage of 4.9 h·night^{-1} compared with 1.75 h·night^{-1} in the Canadian study [19]. This suggests that the comparative effectiveness of telemonitoring for improving CPAP compliance is dependent on the baseline compliance of patients in whom telemonitoring is utilised.

Other trials have explored different telemedicine approaches to improve CPAP compliance, including teleconsultation with a physician [22], periodic automated calls retrieving patient's self-reported information [23], daily internet-based informational support and feedback [24], and telehealth sessions with a nurse [25]. However, the results of these trials were inconsistent, thus reinforcing the idea of the additional efficacy of telemonitoring strategies being highly dependent on the baseline characteristics and compliance of the target population, as well as the proposed telemedicine intervention.

TABLE 3 Patient satisfaction after 3 months of follow-up

	Standard care	Telemedicine	p-value	
			Unadjusted[#]	Adjusted[¶]
Subjects	48	52		
Overall satisfaction			0.006	0.034
Low/moderate	2 (4)	11 (26)		
High/very high	45 (96)	32 (74)		
Feeling of appropriate contact with the hospital			0.015	0.054
Low/moderate	2 (4)	11 (22)		
High/very high	45 (96)	39 (78)		
Telemonitoring assessment				
Usefulness				
Low/moderate		16 (37)		
High/very high		27 (63)		
Ease of use				
Low/moderate		18 (39)		
High/very high		28 (61)		
Privacy protection				
Low/moderate		41 (85)		
High/very high		7 (15)		
Usefulness of online information				
Low/moderate		9 (19)		
High/very high		39 (81)		

Data are presented as n or n (%), unless otherwise stated. Numbers of subjects may vary slightly in each row due to missing values. [#]: unadjusted p-values determined using the t-test or Fisher's exact test as appropriate; [¶]: adjusted p-values based on linear or logistic regression models adjusted for age, sex, apnoea–hypopnoea index, Epworth Sleepiness Scale score, dyslipidaemia, waist/hip ratio and nocturnal motor activity.

A key aspect of any new treatment strategy, including telemedicine, is the cost of the intervention and its cost-effectiveness. In the current study, both direct and indirect costs were included in a cost-effectiveness analysis, which showed that the telemonitoring strategy used was less expensive and more cost-effective

TABLE 4 Within-trial treatment and follow-up costs (average cost per randomised patient)

	Standard care	Telemedicine	Difference		ICER (EUR per QALY)
			EUR	p-value[#]	
Subjects	48	52			
Direct costs EUR					
Telemonitoring[¶]	0	23.75	−23.75	<0.001	
Sleep unit visits and consultations	69.25	6.73	62.52	<0.001	
CPAP provider visits and consultations	14.38	20.39	−6.01	0.003	
Changes in CPAP device components	79.52	69.13	10.39	0.315	
Total	163.15	119.99	43.16	0.012	
Indirect costs EUR					
Patient travel costs to sleep unit	6.49	0.18	6.31	<0.001	
Patient travel costs to CPAP provider	1.33	3.48	−2.15	0.027	
Total	7.82	3.66	4.16	0.002	
Average total cost per patient EUR	170.97	123.65	47.32	0.022	17358.65

Data are presented as n, unless otherwise stated. Costs based on the Catalan Institute of Health [20] or supplied by the CPAP provider. ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year; CPAP: continuous positive airway pressure. [#]: Mann–Whitney two-sample statistic; [¶]: including 2G (GSM/GPRS) daily data transfer and alarm management costs.

than standard management. Although other telemedicine interventions to improve CPAP compliance have been shown to be less costly than standard care [22], this is the first CPAP compliance telemonitoring trial to specifically report cost-effectiveness. The main source of savings in the telemedicine arm was the reduction in planned monitoring visits, which were partially replaced by a remote intervention. The combination of lower management costs and similar compliance compared with standard care meant that the intervention was cost-effective.

We expected that a reduction in the number of clinic/hospital visits combined with easy monitoring would be appreciated by patients. However, although patient satisfaction was high in both groups, it was significantly higher in the standard management group. Several factors may have contributed to this finding. First, patients willing to participate in a clinical trial are usually highly motivated and thus may be less concerned about avoiding hospital visits than an average patient. Second, contact with the CPAP provider rather than with a hospital physician could be seen to be less satisfactory by some patients. Finally, as reported in the specific telemonitoring questionnaire, some patients reported concerns about their privacy, either because they were contacted due to low compliance or because their compliance data were held by non-hospital-based medical personnel. However, most patients placed a positive value on the usefulness of online information and telemonitoring. Therefore, there is obviously room for improvement regarding patient satisfaction with the telemedicine strategy used in this study. We hypothesise that there may be an initial barrier preventing patients from fully embracing and feeling comfortable with telemonitoring. It would therefore appear that better ways of educating patients about telemonitoring are required to ensure that they have an adequate understanding of both the suitability of the telemonitoring approach for the management of CPAP compliance and the protection of privacy, especially for patients who might be more attached to their hospital physician or more concerned about privacy issues. This could improve patient satisfaction with telemonitoring strategies.

Savings generated by use of the telemedicine approach, *via* avoidance of planned visits to the sleep unit, were significant and had an important impact in terms of cost-effectiveness. Moreover, telemonitoring could facilitate a reduction of the care burden at sleep units that are already operating at, or close to, maximum capacity.

The current study has several strengths, including the novelty of the 2G (GSM/GPRS) telemonitoring strategy, utilisation of the same CPAP devices in both study arms, inclusion of a broad range of effect measures (*i.e.* compliance, changes in symptoms and changes in QoL), evaluation of patient satisfaction, and the inclusion of cost and cost-effectiveness analyses. However, there are also some limitations that need to be taken into account. First, the assessment of patient satisfaction was performed using a nonvalidated questionnaire. The high level of compliance in the standard management group could have masked any potential benefits of telemonitoring. The exclusion of patients with other associated sleep disorders (periodic limb movements or other parasomnias), severe comorbidities (*e.g.* respiratory or cardiovascular diseases) and central sleep apnoea limits the generalisability of the current results to patients with pure OSA. Such patients are likely to be the ideal population for telemonitoring programmes. However, patients with more complex presentations are likely to benefit the most from standard management including close follow-up in sleep units. All cost analyses are highly dependent on the characteristics of the healthcare setting in which they are conducted. Therefore, extrapolation of the results to different settings should be done cautiously. Moreover, the possibility of unrealistic pricing of the supplied telemonitoring services cannot be completely ruled out, although sensitivity analyses increasing such costs by 25% and 50% were performed. Finally, the short follow-up period of this study (3 months) does not allow the extrapolation of the results to the long term.

Conclusions

In this study telemonitoring was not able to improve CPAP treatment compliance. Moreover, telemonitoring was associated with lower patient satisfaction compared with standard care. However, for the first time, telemonitoring was shown to be more cost-effective than standard care for the management of OSA, reducing the number of scheduled visits to the sleep unit. An extended follow-up period is needed to evaluate the long-term reproducibility of these results.

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Author contributions: C. Turino and J. de Batlle had full access to all of the data in the study and take responsibility for the content of the manuscript, including the integrity of the data. M. Sánchez-de-la-Torre and F. Barbé conceived and designed the study. C. Turino, A. Mayoral, A.L. Castro-Grattoni, S. Gómez and M. Dalmases were involved in the data acquisition. J. de Batlle analysed the data. C. Turino and J. de Batlle wrote the first draft of the manuscript. C. Turino, J. de Batlle, H. Woehrle, M. Sánchez-de-la-Torre and F. Barbé contributed to the interpretation of the data and clinical

inputs. All authors were involved in the revision of the manuscript for important intellectual content and approved the final version to be published.

References

1 Peppard PE, Young T, Barnet JH, *et al.* Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol* 2013; 177: 1006–1014.
2 Sánchez-de-la-Torre M, Campos-Rodriguez F, Barbé F. Obstructive sleep apnoea and cardiovascular disease. *Lancet Respir Med* 2013; 1: 61–72.
3 Marin JM, Agustí A, Villar I, *et al.* Association between treated and untreated obstructive sleep apnea and risk of hypertension. *JAMA* 2012; 307: 2169–2176.
4 Cano-Pumarega I, Duran-Cantolla J, Aizpuru F, *et al.* Obstructive sleep apnea and systemic hypertension: longitudinal study in the general population. *Am J Respir Crit Care Med* 2011; 184: 1299–1304.
5 Gottlieb DJ, Yenokyan G, Newman AB, *et al.* Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the Sleep Heart Health Study. *Circulation* 2010; 122: 352–360.
6 Terán-Santos J, Jiménez-Gómez A, Cordero-Guevara J. The association between sleep apnea and the risk of traffic accidents. Cooperative Group Burgos-Santander. *N Engl J Med* 1999; 340: 847–851.
7 Barbé F, Pericás J, Muñoz A, *et al.* Automobile accidents in patients with sleep apnea syndrome. An epidemiological and mechanistic study. *Am J Respir Crit Care Med* 1998; 158: 18–22.
8 Giles TL, Lasserson TJ, Smith BH, *et al.* Continuous positive airways pressure for obstructive sleep apnoea in adults. *Cochrane Database Syst Rev* 2006; 3: CD001106.
9 Kribbs NB, Pack AI, Kline LR, *et al.* Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. *Am Rev Respir Dis* 1993; 147: 887–895.
10 Barbé F, Durán-Cantolla J, Capote F, *et al.* Long-term effect of continuous positive airway pressure in hypertensive patients with sleep apnea. *Am J Respir Crit Care Med* 2010; 181: 718–726.
11 Durán-Cantolla J, Aizpuru F, Montserrat JM, *et al.* Continuous positive airway pressure as treatment for systemic hypertension in people with obstructive sleep apnoea: randomised controlled trial. *Br Med J* 2010; 341: c5991.
12 Barbé F, Durán-Cantolla J, Sánchez-de-la-Torre M, *et al.* Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial. *JAMA* 2012; 307: 2161–2168.
13 Martínez-García MA, Capote F, Campos-Rodríguez F, *et al.* Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: the HIPARCO randomized clinical trial. *JAMA* 2013; 310: 2407–2415.
14 Sawyer AM, Gooneratne NS, Marcus CL, *et al.* A systematic review of CPAP adherence across age groups: clinical and empiric insights for developing CPAP adherence interventions. *Sleep Med Rev* 2011; 15: 343–356.
15 Hussain S, Irfan M, Waheed Z, *et al.* Compliance with continuous positive airway pressure (CPAP) therapy for obstructive sleep apnea among privately paying patients – a cross sectional study. *BMC Pulm Med* 2014; 14: 188.
16 Campos-Rodriguez F, Martinez-Alonso M, Sanchez-de-la-Torre M, *et al.* Long-term adherence to continuous positive airway pressure therapy in non-sleepy sleep apnea patients. *Sleep Med* 2016; 17: 1–6.
17 Rolfe I, Olson LG, Saunders NA. Long-term acceptance of continuous positive airway pressure in obstructive sleep apnea. *Am Rev Respir Dis* 1991; 144: 1130–1133.
18 McArdle N, Devereux G, Heidarnejad H, *et al.* Long-term use of CPAP therapy for sleep apnea/hypopnea syndrome. *Am J Respir Crit Care Med* 1999; 159: 1108–1114.
19 Fox N, Hirsch-Allen AJ, Goodfellow E, *et al.* The impact of a telemedicine monitoring system on positive airway pressure adherence in patients with obstructive sleep apnea: a randomized controlled trial. *Sleep* 2012; 35: 477–481.
20 Government of Catalonia. Official Journal of the Government of Catalonia Document CVE-DOGC-A-13051031-2013. www20.gencat.cat/portal/site/portaldogc Date last accessed: June 6, 2016.
21 Weinstein MC, Stason WB. Foundations of cost-effectiveness analysis for health and medical practices. *N Engl J Med* 1977; 296: 716–721.
22 Isetta V, Negrín MA, Monasterio C, *et al.* A Bayesian cost-effectiveness analysis of a telemedicine-based strategy for the management of sleep apnoea: a multicentre randomised controlled trial. *Thorax* 2015; 70: 1054–1061.
23 Sparrow D, Aloia M, Demolles DA, *et al.* A telemedicine intervention to improve adherence to continuous positive airway pressure: a randomised controlled trial. *Thorax* 2010; 65: 1061–1066.
24 Taylor Y, Eliasson A, Andrada T, *et al.* The role of telemedicine in CPAP compliance for patients with obstructive sleep apnea syndrome. *Sleep Breath* 2006; 10: 132–138.
25 Smith CE, Dauz ER, Clements F, *et al.* Telehealth services to improve nonadherence: a placebo-controlled study. *Telemed J E Health* 2006; 12: 289–296.

5.4 ARTICLE 4

"Management and treatment of patients with obstructive sleep apnea using an Intelligent Monitoring System based on machine-learning aiming to improve continuous positive airway pressure (CPAP) treatment compliance: a Randomized Controlled Trial"

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Submitted

Original Paper

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Management and treatment of patients with obstructive sleep apnea using an Intelligent Monitoring System based on machine-learning aiming to improve continuous positive airway pressure (CPAP) treatment compliance: a Randomized Controlled Trial

Abstract

Background: Continuous positive airway pressure (CPAP) is an effective treatment for obstructive sleep apnea (OSA), but treatment compliance is often unsatisfactory.

Objective: To assess the effectiveness and cost-effectiveness of an Intelligent Monitoring System for improving CPAP compliance.

Methods: Prospective, open label, parallel, randomized controlled trial including 60 newly-diagnosed OSA patients requiring CPAP (apnea-hypopnea index >15) from Lleida, Spain. Participants were randomized (1:1) to standard management or the MiSAOS Intelligent Monitoring System, consisting on: (i) early compliance detection, thus granting measures of patient's CPAP compliance from the very first days of usage; (ii) machine-learning-based prediction of mid-term future CPAP compliance; and, (iii) rule-based recommendations for the patient (App) and care team. Clinical and anthropometric variables, daytime sleepiness and quality of life were recorded at baseline and after 6 months, together with patient's compliance, satisfaction, and healthcare costs.

Results: Randomized patients had mean (SD) age 57 (11) years, apnea-hypopnea index 50 (27), and 13% were women. Patients in the intervention arm had a mean (95% CI) of 1.14 (0.04 to 2.23) h/day higher adjusted CPAP compliance than controls ($P = 0.047$). Patients' satisfaction was excellent in both arms, and up to 88% of intervention patients reported willingness to keep using MiSAOS App in the future. No significant differences were found in costs (control: mean (SD) 90.2€ (53.1); intervention: mean (SD) 96.2€ (62.13); $P = 0.688$). Overall costs combined with results on compliance demonstrated cost-effectiveness in a bootstrap-based simulation analysis.

Conclusions: A machine-learning-based Intelligent Monitoring System increased daily compliance, reported excellent patient satisfaction similar to that reported in usual care, and did not incur in a substantial increase

in costs, thus proving cost-effectiveness. This study supports the implementation of intelligent eHealth frameworks for the management of CPAP-treated OSA patients and confirms the value of patients' empowerment in the management of chronic diseases.

Trial registration: ClinicalTrials.gov NCT03116958.

Keywords: obstructive sleep apnea; continuous positive airway pressure; patient compliance; remote monitoring; machine learning

Introduction

Obstructive sleep apnea (OSA) is the most prevalent sleep disordered breathing condition, affecting 15-30% of adults in western countries [1]. It is characterized by repetitive episodes of airways collapse during sleep, causing sleep fragmentation, intermittent hypoxia and daytime somnolence. OSA has been associated with increased morbidity and mortality, and has an impact on quality of life (QoL) [2]. In this sense, increased inflammation, oxidative stress, sympathetic activation and hypercoagulability are the main mechanisms associating OSA with hypertension; cancer; and cardiovascular, cerebrovascular and metabolic diseases [2].

Nocturnal continuous positive airway pressure (CPAP), preventing upper airway collapse during sleep, is the treatment of choice for symptomatic OSA patients [3]. A satisfactory CPAP compliance ($\geqslant$4 h·day^{-1}) improves daytime sleepiness and overall quality of life; reduces OSA severity markers, such as the apnea-hypopnea index (AHI); moderately decreases arterial blood pressure, mainly in patients with resistant hypertension [3,4]; and, contributes to preventing the onset of newly-diagnosed hypertension [5]. Compliance is, therefore, essential for the efficacy of CPAP treatment and its optimization is an important aspect of patient management. However, up to one third of patients underuse or even discontinue CPAP [6-8], mostly because of treatment-related side effects like machine noise, pressure intolerance, mask displacement or claustrophobia [9]. In this sense, issues hampering CPAP compliance during the first months of treatment are likely to have a significant impact on long-term CPAP compliance [10]. Therefore, there is a need to implement effective strategies for the promotion of CPAP compliance, especially during the first months of treatment.

Up to date, interventions tackling CPAP compliance consisting on novel educational, supportive or therapeutic strategies have reported low to moderate evidence of success [11,12]. In contrast, when these strategies are wrapped-up in comprehensive packages making use of information and communication technologies (eHealth) and targeting the initial months after CPAP prescription, the potential for success can be significantly enhanced [12-14]. In this scenario, and within the frame of the MiSAOS project, an Internet of Things (IoT)-based Intelligent Monitoring System relying on machine learning [15] was developed in Catalonia , Spain, with

a fourfold goal: (i) predicting patient's potential early CPAP compliance; (ii) providing real-time monitoring of patient's CPAP compliance, informing both the patient and the care team, and granting decision support; (iii) empowering the patient by means of feedback and recommendations; and, (iv) reducing patient's overall management costs. The current manuscript compares in terms of effectiveness and cost-effectiveness the MiSAOS Intelligent Monitoring System model, based on early compliance detection, compliance prediction and rule-based recommendations, with the usual care provided to patients using CPAP in the region of Lleida, Catalonia.

Methods

Study design

Prospective, open label, parallel, randomized controlled trial comparing the MiSAOS management model with care as usual for a duration of six months after CPAP prescription (ClinicalTrials.gov NCT03116958). The study was conducted from November 2016 to December 2017 in Lleida, Catalonia.

Target population

OSA patients (apnea-hypopnea index (AHI) ≥ 15) being newly diagnosed in the Sleep Unit (SU) of University Hospital Santa Maria, Lleida, and requiring CPAP treatment according to the Spanish Respiratory Society (SEPAR) guidelines [16]. The specific eligibility criteria were: having 18+ years; having a sufficient competence in the use of smartphones; not having been previously treated with CPAP; not having impaired lung function (overlap syndrome, obesity hypoventilation syndrome, and restrictive disorders), severe heart failure, severe chronic pathologies, psychiatric disorders, or periodic leg movements or other dyssomnias or parasomnias; and not being pregnant.

Sample size

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 29 subjects per study arm were needed to recognize as statistically significant a difference in compliance greater than or equal to 1 hour/day. The common standard deviation was assumed to be 1.35, based on previous research of the group.

Recruitment, randomization and intervention

Patients were recruited in the SU and randomized (1:1) to six months of MiSAOS or usual care management. Patients in the usual care arm were managed according to the SEPAR guidelines [16]. Randomization was based on a permuted block design with a computer random number generator and a fixed block size of 4. Patients were fitted with a mask and given a CPAP device (AirSense 10; ResMed, Sydney, Australia) and a leaflet explaining how to use it. A short training session on how to use a CPAP device was also given to patients and partners in the sleep unit by a trained nurse with experience in the follow-up of CPAP-treated patients. This included a practical demonstration of how to put on the mask, and the correct management and cleaning of the tubes, mask and humidifier. Information on how to turn the CPAP device on and off was provided by the homecare provider at the time of machine delivery. As per SEPAR recommendations, patients were visited after 1 month of treatment by the specialist nurse at the sleep unit. Information about CPAP pressure, compliance (use of CPAP for $\geqslant$4 h·day^{-1}), residual respiratory events and leaks were downloaded from the device. CPAP-related side effects, CPAP machine care and maintenance actions (i.e. changes of mask), and the number of required additional visits and/or calls were recorded by the nurse.

Similarly, patients in the MiSAOS arm were fitted with a mask, a CPAP device (AirSense 10; ResMed, Martinsried, Germany), and a leaflet explaining its use. Patients received the same training sessions from the same personnel as in the usual care arm. However, these patients' CPAP devices were equipped with mobile 2G (GSM/GPRS) technology capable of sending daily information on CPAP compliance, CPAP pressures, mask leaks and residual respiratory events to the MiSAOS–Oxigen Salud web database. Additionally, patients in the MiSAOS arm had access to an integrated platform composed by a website (www.misaos.com) and a mobile app (MiSAOS, available in Android and iOS), benefitting from continuous monitoring and personalized feedback. Sample screenshots of the MiSAOS app showing its main functionalities and features are available

in the online supplement (Figure S1). Similarly, sample screenshots of the MiSAOS website showing some of its functionalities and features are available in the online supplement (Figure S2). Hospital lung specialists managing these patients and the CPAP provider (Oxigen Salud) had also access to the MiSAOS website that provided relevant information and decision support according to the specific role and access-rights of each professional user. Finally, the cloud-based MiSAOS platform connected all the devices for data exchange and hosted an Intelligent Monitoring System, based on machine learning, capable of predicting the expected compliance with the therapy by a given patient and, thus, provide adequate feedback and propose personalized interventions to increase compliance [15,17]. Predictions of patient mid-term compliance were based on patient's characteristics, such as anthropometric data and clinical information, and early compliance data. Examples of the needed information and provided outcome can be found in the online supplement (Figure S2). Based on these predictions, patients were classified in two groups: low compliance and medium/high compliance, and recommendations were provided based on these classes. In brief, recommendations consisted on warnings and exhortation to do better, in case of low compliance, or positive reinforcement messages in case of good compliance, highlighting the key areas to be improved regardless of the compliance. This platform was also used for the monitoring of patient compliance, prompting actions when compliance was too low.

Regardless of study arm, all patients were visited at 3 and 6 months at the SU. Patients were checked about progress and compliance with therapy and any problems with their machine.

Data collection

Baseline information was collected by SU personnel during recruitment, regardless of study arm. This included: age; gender; socioeconomic level; Epworth sleepiness scale (ESS); Quality of Life (EQ-5D); lifestyle habits (tobacco and alcohol consumption); comorbidities; use of medications; weight; height; body mass index (BMI); neck, waist and hip circumference; and, blood pressure (BP). Variables of the sleep study were also recorded including: registration time; sleep duration; Apnea Hypopnea index (AHI); and percentage of nighttime spent with an Oxygen saturation <90% (TC90).

At 3 and 6 months all patients, regardless of study arm, were visited at the SU. Patients were checked about progress and compliance with therapy and any problems with their CPAP machine. These visits included the collection of treatment compliance (number of hours/day); ESS; OSA-related symptoms; EQ-5D; BP; and, anthropometric variables. Additionally, information on CPAP pressure, residual respiratory events and leaks, CPAP-related side effects (mask allergies and skin irritations, dry mouth, congestion, runny nose, sneezing, sinusitis, nosebleeds, and discomfort), overall satisfaction with the therapy (questionnaire), CPAP machine care and maintenance actions (i.e. changes of mask), and the number of any additional visits and calls required by the patient during the follow-up were recorded. Finally, costs for each component, use of services and visits were computed based on standard prices of the CPAP provider and on Catalan Health Department official data (CVE-DOGC-A-13051031-2013) [18]. Only direct costs were considered.

Statistical analyses

T-test, or equivalent non-parametric test, or χ^2 test were used for baseline bivariate analyses, depending on variables' characteristics. Differences in the primary and secondary outcomes between the Intervention and control groups at six months were assessed using ordinary least-squares linear models. All models were adjusted by age, and models for secondary outcomes were further adjusted by the baseline values. A two-sided p value and 95% CI were used. The cost-effectiveness analysis was performed using the total costs for each arm based on intervention effectiveness (CPAP treatment compliance). A probabilistic sensitivity analysis was performed using the bootstrap method, which was represented in a cost-effectiveness plan.

The primary and secondary analyses were performed on both the intention-to-treat (ITT) and per-protocol (PP) samples. The ITT sample included all the patients who were randomized. The PP sample excluded the patients who were lost during the follow-up period. Missing data were imputed using multiple imputation consisting of chained equations, for which 10 complete databases were obtained. The R package 'mice' was used for these calculations. All statistical analyses and data processing procedures were performed using R software, version 3.4.4.

Ethical considerations

This study was approved by ethics committee of Hospital Arnau de Vilanova (CEIC-1283) and all patients provided written informed consent. This project was registered in www.clinicaltrials.gov (ref. NCT03116958).

Results

A total of 60 patients were randomized to MiSAOS (intervention, n = 30) or usual care (control, n = 30) management, 30 in each arm, and up to 53 patients completed the study (Figure 1). Patients' baseline characteristics in both study arms are shown in Table 1 and show that only age was statistically different among groups.

Table 1. Patients' baseline characteristics

	Control (n = 30)	**Intervention (n = 30)**	***P***
Gender (male)	26 (86.7%)	26 (86.7%)	0.999
Age (years)	58 (10)	52 (12)	0.039
Weight (kg)	97 (19)	101 (23)	0.423
BMI (kg/m^2)	33.1 (6.4)	34.7 (7.3)	0.382
Median Systolic BP (mm Hg)	138 (17)	142 (20)	0.422
Median Diastolic BP (mm Hg)	87 [79 to 96]	88 [81 to 95]	0.739
AHI (events/h)	39 [25 to 71]	53 [35 to 65]	0.223

Median [IQR] for quantitative and n (%) for qualitative data. T-test, or equivalent non-parametric test, or χ^2 depending on variables' characteristics. Quantitative variables are described as mean (Standard Deviation) or Median [Interquartile Range].

BMI: body mass index; BP: blood pressure; AHI: Apnea Hypopnea index.

Table 2 shows the primary and secondary outcomes of the trial according to an ITT analysis. After 6 months, the mean (95% CI) CPAP compliance was 4.89 (4.05 to 5.72) h/day in the control group and 5.79 (5.20 to 6.38) h/day in the intervention group, with an adjusted difference of 1.14 (0.04 to 2.23; p = 0.047) h/day in benefit of intervention. Furthermore, the intervention arm had a higher proportion of patients with good compliance (use of CPAP for $\geqslant$4 h·day^{-1}) than the control arm (88.5% vs 70.4%, respectively; p = 0.199), although this did not achieve statistical significance. Regarding secondary outcomes, ESS, BP and the EQ-5D visual analog scale improved after 6 months of CPAP treatment in both arms, although the change in systolic BP was significantly higher in patients in the control arm than patients in the intervention arm (adjusted *P* = 0.044). Results on a per protocol approach were similar and are shown in the online supplement (Table S1).

Table 2. Differences in primary and secondary outcomes of the trial according to an intention-to-treat analysis.

	Control (n = 30) Mean (SD)	**Intervention (n = 30) Mean (SD)**	**Difference Mean (95% CI)**
Primary Outcome			
Compliance (hours/day)	4.89 (2.30)	5.79 (1.60)	

Crude difference			0.90 (-0.16 to 1.96)
Adjusted difference			1.14 (0.04 to 2.23)
Secondary Outcomes			
ESS (0-24)			
Baseline	10.9 (5.35)	11.1 (5.35)	
6 months	4.90 (2.41)	5.85 (3.91)	
Change	-5.98 (4.42)	-5.22 (4.78)	
Crude difference			0.76 (-1.64 to 3.16)
Adjusted difference			1.05 (-0.51 to 2.61)
Weight (kg)			
Baseline	97.0 (18.6)	101 (22.5)	
6 months	98.2 (20.2)	100 (20.7)	
Change	1.26 (7.86)	-0.95 (7.91)	
Crude difference			-2.21 (-6.98 to 2.56)
Adjusted difference			-2.55 (-7.41 to 2.32)
BMI (kg/m^2)			
Baseline	33.3 (6.20)	34.7 (7.17)	
6 months	34.2 (6.80)	34.8 (6.32)	
Change	0.98 (3.26)	0.14 (3.16)	
Crude difference			-0.84 (-2.95 to 1.27)
Adjusted difference			-0.82 (-2.97 to 1.32)
Systolic BP (mm Hg)			
Baseline	138 (17.0)	142 (19.4)	
6 months	131 (12.7)	138 (17.2)	
Change	-7.02 (15.2)	-3.80 (12.7)	

Crude difference			3.22 (-5.03 to 11.47)
Adjusted difference			7.81 (0.57 to 15.05)
Diastolic BP (mm Hg)			
Baseline	87.7 (13.5)	90.3 (12.5)	
6 months	81.6 (8.84)	86.8 (9.23)	
Change	-6.13 (11.4)	-3.52 (10.6)	
Crude difference			2.61 (-4.04 to 9.27)
Adjusted difference			4.52 (-0.65 to 9.69)
EQ-5D HUI (0-1)			
Baseline	0.84 (0.22)	0.85 (0.17)	
6 months	0.80 (0.19)	0.86 (0.20)	
Change	-0.04 (0.17)	0.00 (0.18)	
Crude difference			0.05 (-0.05 to 0.15)
Adjusted difference			0.03 (-0.06 to 0.13)
EQ-5D VAS (0-10)			
Baseline	4.93 (3.41)	4.63 (3.55)	
6 months	7.35 (1.71)	8.03 (1.32)	
Change	2.42 (2.87)	3.40 (3.65)	
Crude difference			0.98 (-0.72 to 2.69)
Adjusted difference			0.51 (-0.3 to 1.33)

Ordinary least-squares linear models adjusted by age and baseline value.

ESS: Epworth sleepiness scale; BMI: body mass index; BP: blood pressure; EQ-5D: EuroQoL-5D quality of life; HUI: health utility index; VAS: visual analog scale.

Patients' satisfaction with the management of their illness was excellent in both study groups (Table 3). Similarly, no differences were found in the occurrence of CPAP-related side effects. Finally, all patients in the intervention group reported the MiSAOS app to be useful, 94% of patients reported that it was easy to use, and 88% of patients reported the willingness to continue to use it in the future (Table 3).

Table 3. Overall patients' satisfaction and satisfaction with MiSAOS.

	Control	**Intervention**	
	N (%) or Mean (SD)	**N (%) or Mean (SD)**	***P***
Overall satisfaction	**(n = 26)**	**(n = 19)**	
The follow-up I received was sufficient to manage my health and medical needs			
Agrees / strongly agrees	26 (100%)	19 (100%)	
Overall score [1-7]	6.38 (0.80)	6.53 (0.61)	0.506
In general I am satisfied with the management of my illness			
Agrees / strongly agrees	26 (100%)	19 (100%)	
Overall score [1-7]	6.62 (0.57)	6.53 (0.61)	0.623
My contact with the hospital was sufficient			
Agrees / strongly agrees	26 (100%)	18 (95%)	
Overall score [1-7]	6.62 (0.64)	6.21 (1.62)	0.313
Satisfaction with MiSAOS (intervention only)		**(n=17)**	
The app was useful			
Agrees / strongly agrees		17 (100%)	
Overall score [1-7]		6.53 (0.72)	
The app was easy to use			
Agrees / strongly agrees		16 (94%)	

Overall score [1-7]	6.41 (0.87)
I would like to use the app every day in the future	
Agrees / strongly agrees	15 (88%)
Overall score [1-7]	6.35 (1.17)

Table 4 shows the costs of the intervention, costs of contacts with the CPAP provider and health system (not including the baseline, 3-month, and 6-month visits, as all patients regardless of study arm did them), and costs of any CPAP machine care and maintenance intervention actions (i.e. changes of mask), during the six months of follow-up. The overall mean (SD) cost per patient was 90.2€ (53.14) in the control group and 96.2€ (62.13) in the intervention group, resulting in a non-significant cost difference between arms. The main differences between arms were the 49.5€ of the intervention costs (2G (GSM/GPRS) daily data transfer and Activation and maintenance costs) in the MiSAOS arm, and the 41€ on Sleep Unit visits in the usual care arm. This overall cost, combined with the results on CPAP treatment compliance (primary outcome) demonstrated cost-effectiveness in a bootstrap-based simulation analysis (Figure 2).

Table 4. Within-trial intervention and follow-up costs (average cost per randomized patient).

Concept	**Control (n=30)** €/patient (SD)	**Intervention (n=30)** €/patient (SD)	**Difference** Mean (95%CI)
Intervention costs[a]			
2G (GSM/GPRS) daily data transfer	0 (0)	41.5 (0)	-41.5 (·)

Activation and maintenance	0 (0)	8 (0)	-8 (·)
Follow-up costs			
Sleep Unit visits & consultations[b]	41 (0)	0 (0)	41 (·)
CPAP provider visits & consultations[c]	9.7 (8.9)	10.0 (10.8)	-0.33 (-5.5 to 4.8)
Changes in CPAP device components[c]			
ResMed Mirage Quattro™	12.5 (28.4)	10.0 (32.6)	2.5 (-13.3 to 18.3)
Resmed Mirage™ FX	0.8 (4.4)	3.2 (8.3)	-2.4 (-5.9 to 1.1)
Resmed Mirage™ Micro	0 (0)	1.1 (4.1)	-1.07 (-2.6 to 0.4)
Resmed Swift™ FX	1.5 (8.2)	4.5 (13.7)	-3 (-8.9 to 2.9)
Resmed Airfit™ P10 (without head-gear)	0 (0)	1.3 (7.3)	-1.33 (-4.1 to 1.4)
Philips Respironics Nuance gel	0 (0)	2.45 (13.4)	-2.45 (-7.5 to 2.6)
Resmed Airfit™ F10	15.0 (30.5)	10.0 (25.9)	5 (-9.6 to 19.6)
Resmed Airfit™ P10 (with head-gear)	1.50 (8.22)	0 (0)	1.5 (-1.6 to 4.6)
SleepNet IQ™	2.20 (8.86)	0 (0)	2.2 (-1.1 to 5.5)
SleepNet Ascend™	0 (0)	0.8 (4.4)	-0.8 (-2.4 to 0.8)
Philips Respironics Amara View	5.00 (15.3)	3.3 (18.3)	1.66 (-7.0 to 10.4)
Philips Respironics Comfort Gel Blue	1.00 (5.48)	0 (0)	1 (-1.0 to 3.0)
Total	90.2 (53.1)	96.2 (62.1)	-6.0 (-35.9 to 23.9)

[a] Estimated costs supplied by the CPAP provider: 2G (GSM/GPRS) daily data transfer (83€/year); Activation and maintenance (16€/year).

[b] Not including the baseline, 3-month, and 6-month visits, as all patients did them regardless of study arm. Costs based on the Catalan Institute of Health (CVE-DOGC-A-13051031-2013): Sleep Unit visits & consultations (41€/contact).

[c] Commercial costs supplied by the CPAP provider: CPAP provider visits & consultations (10€/contact); ResMed Mirage Quattro™ (75€/unit); Resmed Mirage™ FX (24€/unit); Resmed Mirage™ Micro

(16€/unit); Resmed Swift™ FX (45€/unit); Resmed Airfit™ P10 (without head-gear) (40€/unit); Philips Respironics Nuance gel (73.5€/unit); Resmed Airfit™ F10 (75€/unit); Resmed Airfit™ P10 (with head-gear) (45€/unit); SleepNet IQ™ (22€/unit); SleepNet Ascend™ (24€/unit); Philips Respironics Amara View (50€/unit); Philips Respironics Comfort Gel Blue (30€/unit).

Discussion

Principal Results

This study is the first randomized controlled clinical trial assessing the effectiveness and cost-effectiveness of a machine-learning-based Intelligent Monitoring System aiming to improve CPAP compliance in OSA patients. The MiSAOS Intelligent Monitoring System, based on early compliance detection, compliance prediction, and rule-based recommendations, was compared to usual care in the region of Lleida, showing a mean increase of 1.14 hours in daily compliance with no substantial differences in direct costs and an excellent patient satisfaction. This novel management system proved to be cost-effective and thus a viable option for the management of OSA patients treated with CPAP.

Strengths and limitations

The current study has several strengths, these included: (i) the use of the same CPAP devices in both study arms; (ii) the use of an Intelligent Monitoring System model, based on early compliance detection, machine-learning-based compliance prediction and rule-based recommendations; (iii) the inclusion of continuous patient feedback through an App; (iv) the measure of a broad range of effect measures (i.e. compliance,

changes in symptoms, and changes in QoL); the assessment of patient comfort and satisfaction; and, (v) the inclusion of cost and cost-effectiveness analyses. Nevertheless, there are also some limitations to be acknowledged: (i) the slight infra-estimation of the required number of study subjects limited the statistical power of some of the between arm comparisons, although this did not affect the results on the primary outcome and cost-effectiveness; (ii) the assessment of patient satisfaction was performed using a non-validated questionnaire; (iii) the exclusion of patients with severe chronic pathologies and other dyssomnias or parasomnias could limit the generalizability of the current results, although the included patients would be the ideal target for eHealth interventions as more complex patients could require a close follow-up in the sleep units; (iv) the results of cost analyses are highly dependent on the characteristics of the healthcare setting in which they are conducted and, thus, extrapolation of the results to different settings should be done cautiously; and, (v) the follow-up period does not allow the extrapolation of results to the long term.

Comparison with existing literature

Patients experiencing the MiSAOS Intelligent Monitoring System showed a mean increase of 1.14 hour in daily CPAP compliance when compared to patients in usual care. This result is more positive than the mean (95% CI) increase of 0.54 (0.29-0.79) hours reported by Aardoom et al in a 2020 meta-analysis including 18 studies with eHealth interventions [14]. Other recent studies exploring advanced monitoring systems have shown similarly inferior results, for instance, Pepin et al reported a 0.53 hours increase in CPAP compliance in OSA patients with high cardiovascular risk using a multimodal telemonitoring intervention [19]. Interestingly, granting patients an easy access to their compliance data has reported successful results in terms of increasing patient compliance [20-22]. Therefore, the combination of an intelligent machine-learning-based monitoring system with the empowerment of patients, based on access to daily compliance and personalized feedback through an App, could represent a significant step forward in the promotion of CPAP compliance.

The impact of the CPAP treatment on secondary outcomes in the MiSAOS intervention was very similar to that obtained in usual care and reports in previous literature [12,19]. Sleepiness, overall quality of life, and BP improvements after 6 months of follow-up were similar in both study arms. The only difference between study

arms was the significantly higher decrease in systolic BP in patients having usual care, which could be easily explained by the baseline differences in BP between study arms.

Patient's comfort and satisfaction are key drivers of compliance with CPAP treatment in the long term [9]. On the one hand, regarding comfort, the number of side effects in both arms was very similar. On the other hand, it must be noticed that in telemedicine interventions patients' satisfaction is usually similar or lower to that of usual care [12], with privacy concerns being the main reported issue [23,24]. In the current trial, all patients reported excellent satisfaction with their management, regardless of study arm. Moreover, patients in the intervention group considered the MiSAOS app as useful and easy to use and reported their willingness to keep using it in the future. These results are better than those obtained in telemonitoring interventions in the same setting (Lleida, Spain) but not providing any direct feedback to the patients [24] and confirm that patient empowerment has a direct impact on patient satisfaction. Finally, potential issues on data privacy had no impact on the current trial results, in contrast to previous research [24], and in line with other interventions providing the patients with regular feedback on compliance [25].

A key aspect of any new management strategy is the cost of the intervention and its cost-effectiveness. In the current study, the analysis of costs and cost-effectiveness showed that the MiSAOS intervention had an overall cost similar to that of usual care while providing better results in terms of treatment compliance, thus demonstrating cost-effectiveness. This result is in contrast to previous cost-effectiveness trials of telemonitoring interventions for CPAP-treated patients in Spain, where cost-effectiveness was demonstrated because of an overall reduction in costs and no significant differences in effectiveness were found [24,26]. Similarly, telemedicine platforms with automated functions to provide education and/or accountability have already shown cost-effectiveness in sleep medicine [22]. This suggests that the addition of machine-learning data processing functionalities together with the empowerment of patients by means of direct feedback, could tip the scales towards significant increases in compliance and boost the cost-effectiveness of already existing telemonitoring interventions. Moreover, it should be noticed that a key factor of telemonitoring is the reduction in the number and/or duration of follow-visits, which was quantified by Anttalainen et al, reporting

a saving of 19 min in nursing time when comparing telemonitoring with usual care in the habituation phase of CPAP treatment (4 weeks) [27], and should be sufficient to mitigate the costs of telemonitoring.

Implications for future clinical practice

As previously stated, the main barriers for the large-scale implementation of novel management interventions are its costs and cost-effectiveness. In the optimal scenario, a novel management strategy should be cheaper than usual care while providing better results. The MiSAOS model has shown the potential to generate better results than usual care in terms of compliance. However, it was not cheaper than usual care. Fortunately, most of the costs of the intervention derived from the use of a 2G (GSM/GPRS) system for daily CPAP compliance data transfer. This technology could be easily replaced by a secure wireless connection to the patients' home Wi-Fi network, which would represent a huge saving and further boost cost-effectiveness. Even in rural areas such as Lleida, this scenario is rapidly becoming a reality and most homes have a suitable Wi-Fi network.

Conclusion

The use of a machine-learning-based Intelligent Monitoring System increased daily compliance, reported an excellent patient satisfaction similar to that reported in usual care, and did not incur in a substantial increase in costs, thus proving cost-effectiveness. This study supports the implementation of intelligent eHealth frameworks for the management of CPAP-treated OSA patients and confirms the value of patients' empowerment in the management of chronic diseases.

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Authors' contributions

CT, EV, JB, FB, and JdB participated in the conceptualization of project. CT, AL, LP, RV, and AC conducted data collection. CT, IDB and AM-M participated in data curation. IDB conducted all statistical analyses. CT, IDB and JdB wrote the original draft of the manuscript. All authors reviewed the final manuscript. JB and FB secured funding for the project.

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Conflicts of interest

None declared.

Abbreviations

AHI: apnea-hypopnea index

BP: blood pressure

BMI: body mass index

CPAP: Continuous positive airway pressure

ESS: Epworth sleepiness scale

ITT: intention-to-treat

IoT: Internet of Things

OSA: obstructive sleep apnea

PP: per-protocol

SU: Sleep Unit

SEPAR: Spanish Respiratory Society

References

1. Senaratna CV, Perret JL, Lodge CJ, Lowe AJ, Campbell BE, Matheson MC, Hamilton GS, Dharmage SC. Prevalence of obstructive sleep apnea in the general population: A systematic review. Sleep Med Rev 2017;34:70-81.

2. Sánchez-de-la-Torre M, Campos-Rodriguez F, Barbé F. Obstructive sleep apnoea and cardiovascular disease. *Lancet Respir Med* 2013; 1:61–72.

3. Iftikhar IH, Bittencourt L, Youngstedt SD, Ayas N, Cistulli P, Schwab R, Durkin MW, Magalang UJ. Comparative efficacy of CPAP, MADs, exercise-training, and dietary weight loss for sleep apnea: a network meta-analysis. Sleep Med 2017;30:7-14.

4. Martínez-García MA, Capote F, Campos-Rodríguez F, Lloberes P, Díaz de Atauri MJ, Somoza M, Masa JF, González M, Sacristán L, Barbé F, Durán-Cantolla J, Aizpuru F, Mañas E, Barreiro B, Mosteiro M, Cebrián JJ, de la Peña M, García-Río F, Maimó A, Zapater J, Hernández C, Grau SanMarti N, Montserrat JM; Spanish Sleep Network. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: the HIPARCO randomized clinical trial. JAMA 2013;310(22):2407-2415.

5. Barbé F, Durán-Cantolla J, Sánchez-de-la-Torre M, Martínez-Alonso M, Carmona C, Barceló A, Chiner E, Masa JF, Gonzalez M, Marín JM, Garcia-Rio F, Diaz de Atauri J, Terán J, Mayos M, de la Peña M, Monasterio C, del Campo F, Montserrat JM; Spanish Sleep And Breathing Network. Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial. JAMA 2012; 307: 2161–2168.

6. Sawyer AM, Gooneratne NS, Marcus CL, Ofer D, Richards KC, Weaver TE. A systematic review of CPAP adherence across age groups: Clinical and empiric insights for developing CPAP adherence interventions. *Sleep Med Rev* 2011; 15: 343–356.

7. Hussain S , Irfan M, Waheed Z , Alam N , Mansoor S, Islam M. Compliance with continuous positive airway pressure (CPAP) therapy for obstructive sleep apnea among privately paying patients - a cross sectional study. *BMC Pulm Med* 2014; 14: 188.

8. Campos-Rodriguez F, Martinez-Alonso M, Sanchez-de-la-Torre M, Barbe F; Spanish Sleep Network. Long-term adherence to continuous positive airway pressure therapy in non-sleepy sleep apnea patients. *Sleep Med* 2016; 17: 1–6.

9. Rolfe I, Olson LG, Saunders NA. Long-term acceptance of continuous positive airway pressure in obstructive sleep apnea. *Am Rev Respir Dis* 1991; 144: 1130–1133.

10. McArdle N, Devereux G, Heidarnejad H, Engleman HM, Mackay TW, Douglas NJ. Long-term use of CPAP therapy for sleep apnea/hypopnea syndrome. Am J Respir Crit Care Med 1999; 159: 1108–1114.

11. Wozniak D, Lasserson TJ, Smith I. Educational, supportive and behavioural interventions to improve usage of continuous positive airway pressure machines in adults with obstructive sleep apnoea. Cochrane Database Syst Rev 2014: CD007736.

12. Bruyneel M. Telemedicine in the diagnosis and treatment of sleep apnoea. Eur Respir Rev 2019; 28(151): 180093.

13. Pépin JL, Tamisier R, Hwang D, Mereddy S, Parthasarathy S. Does remote monitoring change OSA management and CPAP adherence? Respirology 2017; 22(8): 1508-1517.

14. Aardoom JJ, Loheide-Niesmann L, Ossebaard HC, Riper H. Effectiveness of eHealth Interventions in Improving Treatment Adherence for Adults With Obstructive Sleep Apnea: Meta-Analytic Review. J Med Internet Res 2020; 22(2): e16972.

15. Xavier Rafael-Palou, Eloisa Vargiu, Cecilia Turino, Alexander Steblin, Manuel Sánchez-de-la-Torre, Ferran Barbé. Towards an Intelligent Monitoring System for Patients with Obstructive Sleep Apnea. EAI Endorsed Trans Ambient Syst 2017; 16: e1

16. Lloberes P, Durán-Cantolla J, Martínez-García MÁ, Marín JM, Ferrer A, Corral J, Masa JF, Parra O, Alonso-Álvarez ML, Terán-Santos J. Diagnosis and treatment of sleep apnea-hypopnea syndrome. Spanish Society of Pulmonology and Thoracic Surgery. Arch Bronconeumol 2011; 47(3): 143-56.

17. Rafael-Palou X, Turino C, Steblin A, Sánchez-de-la-Torre M, Barbé F, Vargiu E. Comparative analysis of predictive methods for early assessment of compliance with continuous positive airway pressure therapy. BMC Med Inform Decis Mak 2018; 18(1): 81.

18. CVE-DOGC-A-13051031-2013: Resolution SLT/353/2013, of February 13, on the review of public prices for the services provided by the Catalan Health Institute. https://www.comb.cat/Upload/Documents/4635.pdf (last accessed 01/09/2020). [Catalan]

19. Pépin JL, Jullian-Desayes I, Sapène M, Treptow E, Joyeux-Faure M, Benmerad M, Bailly S, Grillet Y, Stach B, Richard P, Lévy P, Muir JF, Tamisier R. Multimodal Remote Monitoring of High Cardiovascular Risk Patients With OSA Initiating CPAP: A Randomized Trial. Chest 2019; 155(4): 730-739.

20. Stepnowsky C, Edwards C, Zamora T, Barker R, Agha Z. Patient perspective on use of an interactive website for sleep apnea. Int J Telemed Appl 2013; 2013: 239382.

21. Kuna ST, Shuttleworth D, Chi L, Schutte-Rodin S, Friedman E, Guo H, Dhand S, Yang L, Zhu J, Bellamy SL, Volpp KG, Asch DA. Web-Based Access to Positive Airway Pressure Usage with or without an Initial Financial Incentive Improves Treatment Use in Patients with Obstructive Sleep Apnea. Sleep 2015; 38(8): 1229-36.

22. Hwang D, Chang JW, Benjafield AV, Crocker ME, Kelly C, Becker KA, Kim JB, Woodrum RR, Liang J, Derose SF. Effect of Telemedicine Education and Telemonitoring on Continuous Positive Airway Pressure Adherence. The Tele-OSA Randomized Trial. Am J Respir Crit Care Med 2018; 197(1): 117-126.

23. Frasnelli M, Baty F, Niedermann J, Brutsche MH, Schoch OD. Effect of telemetric monitoring in the first 30 days of continuous positive airway pressure adaptation for obstructive sleep apnoea syndrome - a controlled pilot study. J Telemed Telecare 2016; 22(4): 209-14.

24. Turino C, de Batlle J, Woehrle H, Mayoral A, Castro-Grattoni AL, Gómez S, Dalmases M, Sánchez-de-la-Torre M, Barbé F. Management of continuous positive airway pressure treatment compliance using telemonitoring in obstructive sleep apnoea. Eur Respir J 2017; 49(2): 1601128.

25. Stepnowsky C, Edwards C, Zamora T, Barker R, Agha Z. Patient perspective on use of an interactive website for sleep apnea. Int J Telemed Appl 2013; 2013: 239382.

26. Isetta V, Negrín MA, Monasterio C, Masa JF, Feu N, Álvarez A, Campos-Rodriguez F, Ruiz C, Abad J, Vázquez-Polo FJ, Farré R, Galdeano M, Lloberes P, Embid C, de la Peña M, Puertas J, Dalmases M, Salord N, Corral J, Jurado B, León C, Egea C, Muñoz A, Parra O, Cambrodi R, Martel-Escobar M, Arqué M, Montserrat JM; SPANISH SLEEP NETWORK. A Bayesian cost-effectiveness analysis of a telemedicine-based strategy for the management of sleep apnoea: a multicentre randomised controlled trial. Thorax 2015; 70(11): 1054-61.

27. Anttalainen U, Melkko S, Hakko S, Laitinen T, Saaresranta T. Telemonitoring of CPAP therapy may save nursing time. Sleep Breath 2016; 20(4): 1209-1215.

Figures

Figure 1. Study flowchart

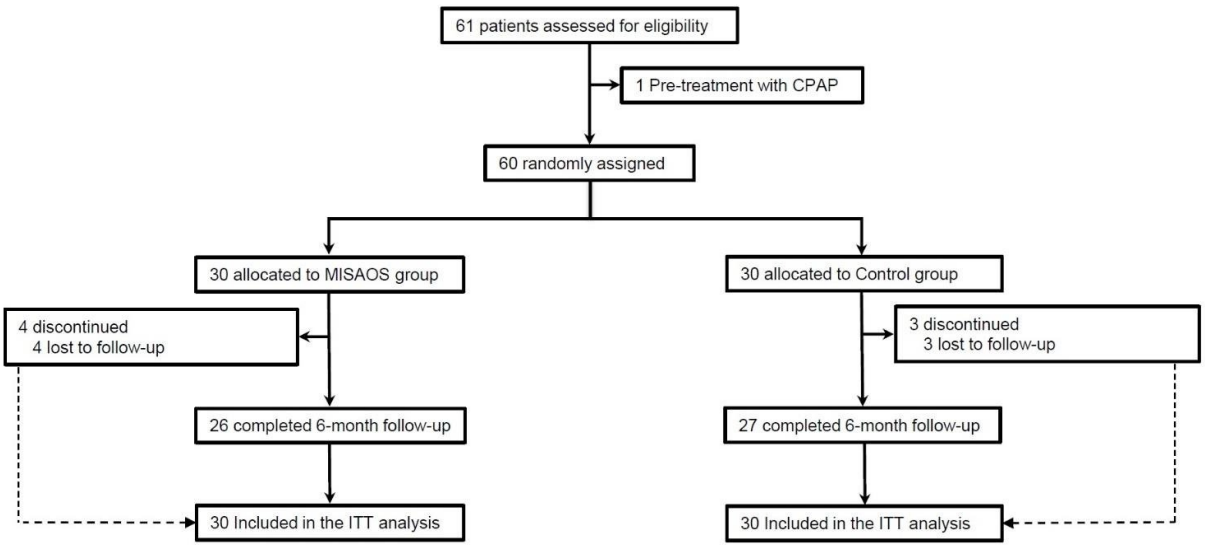
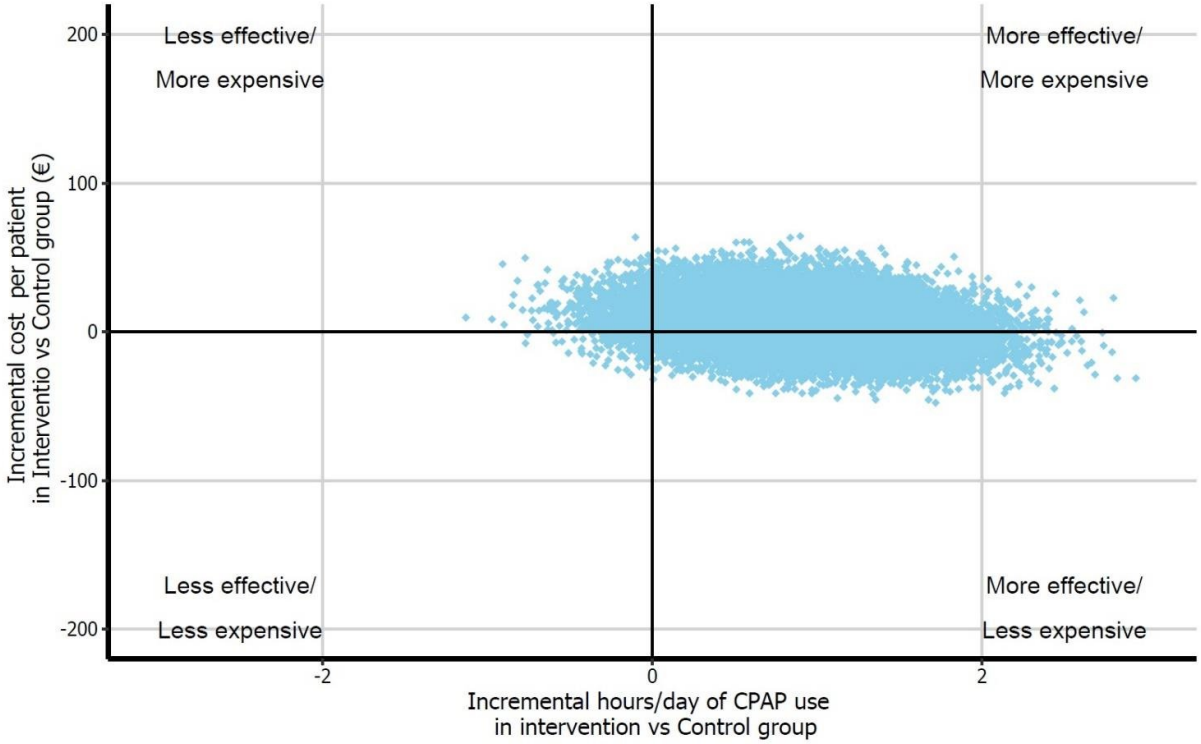


Figure 2. Cost-effectiveness analysis based on treatment compliance (CPAP hours/day) and total costs for each arm, performed using a bootstrap probabilistic sensitivity analysis.



SUPPLEMENTAL INFORMATION

Management and treatment of patients with obstructive sleep apnea using an Intelligent Monitoring System based on machine learning: a randomized controlled trial

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Contents

Screenshots of the MiSAOS App

Screenshot of the MiSAOS app showing : a- intial page ; b- CPAP treatment summary of the last week indicating, in a good compliance: medium daily usage, medium of airleaks, residual AIH . At the bottom positive reinforcement message for the patient, celebrating his good compliance with treatment.
c- at the top: a smile indicates a bad compliance; other images indicate excessive air leaks, bad compliance and residual AHI.
D, E: summary of patients' characteristics and technical details of CPAP treatment.

F-G (en el ppoint): the mobile app provides tools to understand the disease and its treatment, instruction on the functioning of CPAP machine and indication to solve the most common problems that may arise in relation to CPAP use. Patients could choose among FAQs, videos and practical manuals.

Supplementary tables

Table S1. Differences in primary and secondary outcomes of the trial according to a per-protocol analysis.

		Control (n = 30)	Intervention (n=30)	Difference			
				Crude		Adjusted	
		Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	*P*	Mean (95% CI)	*P*
Primary Outcome							
Compliance (hours/day)		4.95 (2.33)	5.68 (1.62)	0.73 (-0.39 to 1.84)	0.196	1.01 (-0.14 to 2.16)	0.085
Secondary Outcomes							
ESS (0-24)							
	Baseline	10.05 (5.28)	11.69 (5.28)				
	6 months	4.73 (2.44)	6.04 (4.12)				
	Change	-5.32 (4.23)	-5.65 (4.78)	-0.33 (-2.84 to 2.19)	0.794	-1.68 (-6.08 to 2.71)	0.443
Weight (kg)							
	Baseline	98.33 (16.00)	100.99 (21.67)				
	6 months	98.58 (17.81)	99.53 (19.51)				
	Change	0.25 (5.94)	-1.46 (7.58)	-1.71 (-5.89 to 2.48)	0.415	-0.25 (-1.87 to 1.37)	0.755
BMI (kg/m^2)							
	Baseline	33.62 (5.52)	34.82 (6.38)				
	6 months	33.93 (6.10)	34.67 (5.36)				

Change	0.31 (2.14)	-0.15 (2.88)	-0.45 (-2.01 to 1.11)	0.561	0.86 (-0.86 to 2.58)	0.32
Systolic BP (mm Hg)						
Baseline	137.77 (17.27)	142.20 (20.02)				
6 months	132.22 (12.20)	140.90 (18.08)				
Change	-7.67 (15.13)	-6.18 (11.22)	1.49 (-6.97 to 9.95)	0.724	7.81 (0.97 to 14.65)	0.026
Diastolic BP (mm Hg)						
Baseline	89.24 (14.01)	92.14 (13.42)				
6 months	82.20 (7.92)	86.53 (9.78)				
Change	-7.04 (11.37)	-5.61 (8.24)	1.43 (-5.01 to 7.88)	0.656	3.52 (-0.94 to 7.98)	0.118
EQ-5D HUI (0-1)						
Baseline	0.82 (0.24)	0.85 (0.18)				
6 months	0.79 (0.19)	0.85 (0.21)				
Change	-0.04 (0.18)	0.01 (0.18)	0.04 (-0.06 to 0.15)	0.398	0.03 (-0.06 to 0.13)	0.475
EQ-5D VAS (0-10)						
Baseline	4.96 (3.52)	4.42 (3.55)				
6 months	7.38 (1.79)	8.00 (1.36)				
Change	2.42 (2.91)	3.58 (3.71)	1.15 (-0.7 to 3.01)	0.218	0.43 (-0.42 to 1.29)	0.309

Ordinary least-squares linear models adjusted by age and baseline value.
ESS: Epworth sleepiness scale; BMI: body mass index; BP: blood pressure; EQ-5D: EuroQoL-5D quality of life; HUI: health utility index; VAS: visual analog scale.

6. DISCUSSION

OSA is a very prevalent disorder with a great impact on the general health system. Due to its burden and consequences on quality of life, OSA represents a socio economic emergency. Nevertheless, the health system has not provided up-to-date and efficient means for dealing with its high prevalence, morbidity and mortality nor for the improvement of efficacy and cost of OSA's most effective treatment: continuous positive airway pressure (CPAP). OSA is, in fact, still widely underdiagnosed in some specific settings like cardiopathic patients, among whom , on the contrary, its recognition has a prognostic value [12,13]. At the same time, a considerable percentage of patients underuse or discontinue CPAP treatment with great repercussions on general health. Although OSA is now regarded as a multi phenotypic disease, strategies for its treatment are still rigid and based on a one-fit-all solution.

With this thesis we investigate the application of a new global approach to OSA management, from the early detection of OSA in a risk population to new modalities of follow-up in order to personalize treatment.

Then, in the first article, we tried to predict the presence of OSA in a specific setting of patients with coronary artery disease. Age, BMI, the ESS, peak troponin levels and usual intake of calcium antagonists were the main determinants of having OSA. Similarly, we identified age, BMI, blood triglycerides, peak troponin levels and having a Killip class II or higher as the main determinants of severe OSA.

In the wake of characterizing patients with OSA to better approach them, in the second article , we performed the first cluster analysis involving the entire CPAP-treated population of Catalonia. Using data from the Catalan Health System, we defined a general profile of OSA patients treated with CPAP, largely represented by middle-aged men, with a high prevalence of hypertension, dyslipidemia, diabetes and obesity. At the same time, cluster analysis identified six patient groups that showed different patterns of comorbidities, mortality, and healthcare resource use.

Finding new methods to improve CPAP compliance and reduce costs of global treatment, in the third article we applied telemonitoring to CPAP treatment follow-up, findig telemonitoring more cost- effective than traditional follow-up.

Finally, in the fourth article, not published yet, we performed the first randomized controlled clinical trial to assess the effectiveness and cost-effectiveness of a machine-learning-based Intelligent Monitoring System (the MiSAOS system) for improving CPAP compliance.

Although quite heterogeneous , this thesis should be read in the context of an ongoing evolution of the global approach to OSA. Multiple randomized trials have been conducted to explore the link between OSA and cardiovascular diseases. And, even more importantly, the real effect of CPAP treatment among specific settings of patients. Using data from ISAAC study, we also tried to deepen this link, searching for a model to predict the presence of undiagnosed OSA among patients admitted for acute coronary syndrome (ACS) that could have a role in the prognosis of patients. Unfortunately, the study failed to create a model to effectively predict OSA among such kinds of patients and only a set of variables associated with OSA (age, BMI and ESS but also peak troponin levels and regular use of calcium antagonists , largey used to treat hypertension) was identified. Furthermore, blood glucose levels but not diabetes was related to the risk of suffering OSA, probably due to diabetes under-diagnosis. Similarly, in a more recent study performed among patients admitted for acute coronary syndrome, the presence of diabetes mellitus, hypertension and class III-IV Mallampati score were more common among patients with moderate-severe OSA compared to no or mild OSA. However, only the presence of diabetes mellitus was found to be an independent risk predictor of diagnosing OSA in patients admitted with ACS [59]. The results of our study were even more disappointing when analyzed in the light of the global results of ISAACC trial that did not show a correlation between OSA and an increased prevalence of cardiovascular events in non sleepy patients admitted for ACS , nor a beneficial effect of CPAP treatment on the prevention of recurrent major cardiovascular events in such group of patients [31]. Nevertheless, no data about symptoms nore clinical features were included in our prediction model, nor in the ISAACC trial. More recent studies have instead suggested a positive effect of CPAP treatment among specific patients phenotypes not investigated in our trials [28]. Despite its negative result, our article has contributed to the knowledge of the complexity of the impact of OSA on cardiopathic patients and represents further evidence of the necessity to better characterize patients for the best treatment.

In the aim to typify OSA patients, we performed a Big Data analysis of the entire CPAP treated population of Catalonia finding six clusters of patients, with different comorbidities, resource use and prognosis. Some aspects of this study must be underlyed: first, this is the first cluster analysis of the entire population of Catalonia and one of the few studies in the world involving the entire

population of a region. However, the lack of clinical data and the differences in the study population, limits the generalizability and comparability of our results with other similar trials. Previous and recent studies on this field, in fact, even with smaller patients' populations, are based on data from national registry, clinical practice and sleep registry analysis of patients suffering from OSA. On the contrary, we did not use data about OSA patients in general, but only about patients with OSA deserving CPAP treatment. Data were provided by the Agency for Health Quality and Assessment of Catalonia (AQuAS) and clinical information was extrapolated from International Classification of Disease version 9 (ICD-9). It is reasonable to assume that our patients population is composed of severe, symptomatic OSA but the absence of specific clinical data and sleep registries does not allow a deeper patients' characterization on the basis of symptoms or sleep alterations. Despite these limitations, we were able to cluster a global population of CPAP treated OSA, with the emblematic results that almost 20% of CPAP treated patients of Catalonia are distributed in cluster 1 and 6 , that is neoplastic and oldest-cardiac cluster respectively. In such a group of patients, perhaps, the presence of OSA plays a limited role in the global prognosis. Thus, also CPAP treatment could have a small impact on life expectancy or quality of life of these patients. In contrast, more than a half of our study population was male, had few comorbidities, and low mortality and healthcare resource use (clusters 2 and 5) with an expected benefit from CPAP treatment. This study fulfills a twofold role: the use of Big Data allows us to deepen the knowledge of OSA phenotypes; furthermore, the results force us to look at OSA and its treatment from a different point of view. That is, not ever indiscriminate treatment for all, but a personalized treatment aimed to obtain the maximum benefit for whom it could be expected. This approach is intended to have a social and economic impact allowing a more careful and effective distribution of medical resources. These conclusions are in line with a recent review by Pepin et al. that argues the role of Big Data in OSA , defining challenges and opportunities of this new approach [60].

In the third article, we presented the second randomised controlled clinical trial to assess the effectiveness of telemonitoring for improving CPAP compliance, the largest to date in terms of the number of enrolled patients, and the first to include cost and cost-effectiveness analyses. Telemedicine did not improve CPAP compliance but was more cost effective than traditional follow-up. It is important to emphasize two points: the first, more general, regarding the usefulness of the information derived from continuous telemonitoring. Linking this information to Big Data analysis, this study represents a further step towards the natural and imperative change of the global vision of OSA already discussed. A second conclusion derived from the result is instead specifically linked

to the article and the costs of telemonitoring. In Europe, an exponential increase in the number of diagnosed OSAS subjects is expected. Two main reasons account for this: 1) the increase in OSAS prevalence in the last decades is associated with increasing prevalence and severity of obesity, the first risk factor for OSAS [61,62]; 2) in EU countries, according to the Commission directive 2014/85/EU, testing for OSAS is mandatory before granting or renewing a driver's license. This way, new methods to reduce the cost of management of OSA are needed.

Our trial was the first one including a cost-effectiveness analysis of telemedicine use in OSA treatment follow- up , perhaps working as a pathfinder in this direction. A more recent clinical trial of Lugo et al., in fact, extended the field of application of telemedicine investigating the cost effectiveness of a global management of OSA, from diagnosis, to treatment and follow-up [63]. Their out-of-hospital Virtual Sleep Unit, constituted by a web platform with different accesses to both patients and doctors, with the use of teleconference and phone calls applied to any patients suspected for OSA, was a cost effective and non inferior option with respect to traditional hospital management. One last point deserves a special comment, since it has probably not been highlighted or tackled enough in the paper: the privacy of telemonitorized patients. Although patient satisfaction was high in both study groups, it was significantly higher in the standard management group and patients in the telemonitoring group complained about their privacy. Already at the beginning of 2000, Kara argued that the transmission of unprotected audio-visual signals, even if compressed, via the Internet, carries the risk that someone could become aware of this information, accidentally or intentionally , and for medical and healthcare applications, security caused the most concern [64]. Rather than this aspect, our patients were worried by the spreading of information of their compliance among non-hospital-based medical personnel. It appears then clear that an additional effort is needed to better organize data management and to educate and reassure patients that their privacy is protected by the safest available technology.

With the last article we tried to overcome the kind of telemedicine so far we deal with, creating a web platform and a mobile application in the aim of a complete control of patients on their own health, with the result of a more cost effective management of OSA.

Different studies have been conducted comparing effectiveness of mobile-app and website approach to OSA management with traditional follow-up , finding higher average CPAP use [65].

A recent trial by Suarez-Giron et al. explored the feasibility of using a web site and a mobile application for the management of CPAP treated OSA [66]. Their app provided information focused on the patient's needs (follow-up questionnaire, frequent problems and recommendation) to offer an automatic problem solving service according to patients' answers. Through the web site, accessible for Sleep Unit personnel only, the answers of patients provided via app could be reviewed and patients requiring assistance could be attended. However, no effectiveness nor cost-effectiveness evaluation compared to traditional follow-up, was provided.

Compared with previous trials, some innovative key aspect of our study should then be stressed: first, our web platform was equipped with an Intelligent Monitoring System, capable of predicting the baseline expected CPAP treatment compliance according to the characteristics and clinical history of patients (comorbidities, anthropometric and clinical variables, medical history, sleep studies results). Then, a machine learning program updated the initial prediction according to the daily compliance of the patients. Via the mobile application, and based on the individualized predicted compliance, a personalized direct feedback about their own compliance and encouragement or warning messages were provided to the patients (Fig.2). Website was accessible to both patients and doctors and variation of CPAP setup could be done according to patients' feedback. Information, tips and advice about the disease and its treatment were also available on both website and mobile app (Fig.2).

With the MiSAOS system, we completely reversed the approach to CPAP treated patients, trying to prevent poor compliance instead of simply correcting it. The knowledge of the expected compliance at baseline, in fact, allows to put in place strategies to change an unfavourable prediction. Furthermore, the continuous feedback through the mobile application allows a complete empowerment of the patients to obtain a better compliance of treatment, as already demonstrated in other trials [55]. As a result, the telemedicine group showed better treatment compliance, compared with the traditional management. Furthermore, the MiSAOS group demonstrated cost-effectiveness too. However, in contrast with the previous article, where cost-effectiveness derived from an overall reduction in costs and no significant differences in effectiveness were found, in this trial the overall cost was similar in both arms, while the telemedicine group showed better treatment compliance. Furthermore, despite being assessed using not validated questionnaires, patients' satisfaction was excellent, regardless of study arm , with no concern about privacy. These data suggest that the addition of machine-learning data processing functionalities, together with

the empowerment of patients by direct feedback, could increase compliance and boost the cost effectiveness of already existing telemonitoring interventions, maintaining a good patient satisfaction.

Overall, the papers presented in this thesis, although with some limitations , represent a further contribution to the comprehension of OSA and a further driver towards a personalized management of OSA and a more judicious resource distribution.

A **B**

Fig. 2: Screenshot of the MiSAOS app showing CPAP treatment summary of the last week indicating, in a good compliance (A): medium daily usage, medium of air leaks, residual AIH . At the bottom a positive reinforcement message for the patient, celebrating his good compliance with treatment. B-at the top: a smile indicates a bad compliance; other images indicate excessive air leaks, bad compliance and residual AHI.

7. CONCLUSIONS

The most relevant conclusions of the presented thesis could be summarised as follow:

Conclusions 1: Age, Body Mass Index , Epworth Sleepiness Scale, peak troponin levels, regular use of calcium antagonists and blood glucose levels seem to be associated with the presence of OSA among patients admitted for acute coronary diseases. However, we were not able to realize a predictive model.

Conclusions 2 : The entire CPAP treated population of Catalonia could be grouped in six clusters of patients with different comorbidities profiles (Neoplastic patients; Metabolic syndrome patients; Asthmatic patients ; Musculoskeletal-joint disorder patients; Patients with few comorbidities and Oldest- cardiac disease patients. In two of these clusters (Neoplastic and Oldest-cardiac patients), the presence of OSA seems not relevant for general prognosis.

Conclusions 3: Telemonitoring did not improve CPAP treatment compliance and was associated with lower patient satisfaction. However, telemonitoring was shown to be more cost-effective than standard care for the follow -up of OSA patients.

Conclusions 4 : The MiSAOS Intelligent Monitoring System demonstrated better compliance, excellent satisfaction, and cost-effectiveness, compared to traditional follow-up.

8. REFERENCES

1. Senaratna CV, Perret JL, Lodge CJ, Lowe AJ, Campbell BE, Matheson MC, Hamilton GS, Dharmage SC. Prevalence of obstructive sleep apnea in the general population: A systematic review. Sleep Med Rev. 2017 Aug;34:70-81.

2. Eckert DJ, Malhotra A. Pathophysiology of adult obstructive sleep apnea. Proc Am Thorac Soc. 2008;5:144-53.

3. White LH, Bradley TD. Role of nocturnal rostral fluid shift in the pathogenesis of obstructive and central sleep apnoea. J Physiol. 2013;591:1179-93.

4. Abboud F, Kumar R. Obstructive sleep apnea and insight into mechanisms of sympathetic overactivity. J. Clin. Invest. 2014; 124: 1454–1457.

5. Westermann D, Lindner D, Kasner M, Zietsch C, Savvatis K, Escher F, et al. Cardiac inflammation contributes to changes in the extracellular matrix in patients with heart failure and normal ejection fraction. Circ Heart Fail 2011;4(1):44-52.

6. Ryan S. Mechanisms of cardiovascular disease in obstructive sleep apnoea. J.Thorac. Dis. 2018; 10: S4201–S4211.

7. Brinker JA, Weiss JL, Lappe DL, Rabson JL, Summer WR, Permutt S, Weisfeldt ML. Leftward septal displacement during right ventricular loading in man. Circulation 1980;61(3): 626-33.

8. Logan AG, Perlikowski SM, Mente A, Tisler A, Tkacova R, Niroumand M, et al. High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. J Hypertens. 2001;19(12):2271–7.

9. Redline S, Yenokyan G, Gottlieb DJ, Shahar E, O'Connor GT, Resnick HE, et al. Obstructive sleep apnea–hypopnea and incident stroke. Am J Respir Crit Care Med. 2010;182(2):269–77.

10. Mehra R, Benjamin EJ, Shahar E, Gottlieb DJ, Nawabit R, Kirchner HL, et al. Association of nocturnal arrhythmias with sleepdisordered breathing. Am J Respir Crit Care Med. 2006;173(8): 910–6.

11. Kanagala R, Murali NS, Friedman PA, Ammash NM, Gersh BJ, Ballman KV, et al. Obstructive sleep apnea and the recurrence of atrial fibrillation. Circulation. 2003;107(20):2589–94.

12. Loo G, Tan AY, Koo CY, et al. Prognostic implication of obstructive sleep apnea diagnosed by post-discharge sleep study in patients presenting with acute coronary syndrome. Sleep Med 2014; 15: 631–636.

13. Lee CH, Sethi R, Li R, et al. Obstructive Sleep Apnea and Cardiovascular Events After Percutaneous Coronary Intervention. Circulation 2016;133:2008-17 .10–13.

14. Lucas E Costa, Carlos Henrique G Uchôa, Rebeca R Harmon, Luiz A Bortolotto, Geraldo Lorenzi-Filho, Luciano F Drager Potential underdiagnosis of obstructive sleep apnoea in the cardiology outpatient setting Heart 2015.

15. Epstein LJ, Kristo D, Strollo PJ, et al. Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine: Clinical guidelines for the evaluation, management and long term care of obstructive sleep apnea in adults. J Clin Sleep Med. 2009;5:263-76.

16. Collop NA, McDowell Anderson W, Boehlecke B, et al. Portable Monitoring Task Force of the American Academy of Sleep Medicine. Clinical guidelines for the use of unattended portable monitors in the diagnosis of obstructive sleep apnea in adult patients.. J Clin Sleep Med. 2007;3:737-47.

17. Kribbs NB, Pack AI, Kline LR, Smith PL, Schwartz AR, Schubert NM, et al. Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. Am Rev Respir Dis 1993; 147(5):887-95.

18. Iftikhar IH, Bittencourt L, Youngstedt SD, Ayas N, Cistulli P, Schwab R, Durkin MW, Magalang UJ. Comparative efficacy of CPAP, MADs, exercise-training, and dietary weight loss for sleep apnea: a network meta-analysis. Sleep Med 2017;30:7-14.

19. Martínez-García MA, Capote F, Campos-Rodríguez F, Lloberes P, Díaz de Atauri MJ, Somoza M, Masa JF, González M, Sacristán L, Barbé F, Durán-Cantolla J, Aizpuru F, Mañas E, Barreiro B, Mosteiro M, Cebrián JJ, de la Peña M, García-Río F, Maimó A, Zapater J, Hernández C, Grau SanMarti N, Montserrat JM; Spanish Sleep Network. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: the HIPARCO randomized clinical trial. JAMA 2013;310(22):2407-2415.

20. Barbé F, Durán-Cantolla J, Sánchez-de-la-Torre M, Martínez-Alonso M, Carmona C, Barceló A, Chiner E, Masa JF, Gonzalez M, Marín JM, Garcia-Rio F, Diaz de Atauri J, Terán J, Mayos M, de la Peña M, Monasterio C, del Campo F, Montserrat JM; Spanish Sleep And Breathing Network. Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial. JAMA 2012; 307: 2161-2168.

21. Jared Streatfeild , David Hillman , Robert Adams , Scott Mitchell , Lynne Pezzullo Cost-effectiveness of continuous positive airway pressure therapy for obstructive sleep apnea: health care system and societal perspectives Sleep . 2019 Dec 24;42(12):zsz181.

22. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet. 2005;365:1046-53.

23. Lévy P, Pépin JL, McNicholas WT. Should all sleep apnoea patients be treated? Yes. Sleep Med Rev. 2002;6:17-26.

24. Bratton DJ, Stradling JR, Barbe F, Kohler M. Effect of CPAP on blood pressure in patients with minimally symptomatic obstructive sleep apnoea: a meta-analysis using individual patient data from four randomised controlled trials. Thorax. 2014;69:1128-35.

25. Jaimchariyatam N, Rodriguez CL, Budur K. Does CPAP treatment in mild obstructive sleep apnea affect blood pressure? Sleep Med. 2010;11:837-42.

26. Mokhlesi B, Hagen EW, Finn LA, Hla KM, Carter JR, Peppard PE Obstructive sleep apnoea during REM sleep and incident non-dipping of nocturnal blood pressure: a longitudinal analysis of the Wisconsin Sleep Cohort. Thorax 2015;70:1062–1069.

27. Zinchuk AV, Jeon S, Koo BB, Yan X, Bravata DM, Qin L, et al. Polysomnographic phenotypes and their cardiovascular implications in obstructive sleep apnoea. Thorax 2018;73:472–480 .

28. Mazzotti DR, Keenan BT, Lim DC, Gottlieb DJ, Kim J, Pack AI. Symptom subtypes of obstructive sleep apnea predict incidence of cardiovascular outcomes. Am J Respir Crit Care Med 2019;200: 493–506.

29. Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J, Thunstro E. Effect of positive airway pressure on cardiovascular outcomes in coronary artery disease patients with nonsleepy obstructive sleep apnea: the RICCADSA randomized controlled trial. Am J Respir Crit Care Med 2016;194:613.

30. McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, et al.; SAVE Investigators and Coordinators. CPAP for prevention of cardiovascular events in obstructive sleep apnea. N Engl J Med 2016;375:919–931

31. Manuel Sánchez-de-la-Torre , Alicia Sánchez-de-la-Torre , Sandra Bertran, Jorge Abad, Joaquín Duran-Cantolla, Valentín Cabriada , Olga Mediano , María José Masdeu , Mari Luz Alonso, Juan Fernando Masa , Antonia Barceló , Mónica de la Peña , Mercè Mayos , Ramón Coloma , Josep M Montserrat , Eusebi Chiner , Salvador Perelló , Gemma Rubinós , Olga Mínguez , Lydia Pascual , Anunciación Cortijo , Dolores Martínez , Albina Aldomà , Mireia Dalmases , R Doug McEvoy , Ferran Barbé. Effect of obstructive sleep apnoea and its treatment with continuous positive airway pressure on the prevalence of cardiovascular events in patients with acute coronary syndrome (ISAACC study): a randomised controlled trial, Spanish Sleep Network Lancet Respir Med 2020 Apr;8(4):359-367.

32. Pien GW, Ye L, Keenan BT, Maislin G, Bjornsdottir E, Arnardottir ES, Benediktsdottir B, Gislason T, Pack AI. Changing faces of obstructive sleep apnea: treatment effects by cluster designation in the Icelandic sleep apnea cohort. Sleep 2018; 41.

33. Pepin JL, Bailly S, Tamisier R. Incorporating polysomnography into obstructive sleep apnoea phenotyping: moving towards personalised medicine for OSA. Thorax 2018; 73: 409–11.

34. McArdle N, Devereux G, Heidarnejad H, et al. Long-term use of CPAP therapy for sleep apnea/hypopnea syndrome. Am J Respir Crit Care Med 1999; 159: 1108–1114.

35. Rolfe I, Olson LG, Saunders NA. Long-term acceptance of continuous positive airway pressure in obstructive sleep apnea. *Am Rev Respir Dis* 1991; 144: 1130–1133.

36. WHO. A health telematics policy in support of WHO's Health-For-All strategy for global health development: report of the WHO group consultation on health telematics, 11–16 December, Geneva, 1997. Geneva, World Health Organization, 1998.

37. Strehle EM, Shabde N. One hundred years of telemedicine: does this new technology have a place in paediatrics? Archives of Disease in Childhood, 2006, 91(12):956–959.

38. Zia S, Fields BG. Sleep telemedicine: An emerging field's latest frontier. Chest. 2016;149:1556–65.

39. Singh J, Badr MS, Diebert W, Epstein L, Hwang D, Karres V, et al. American Academy of Sleep Medicine (AASM) position paper for the use of telemedicine for the diagnosis and treatment of sleep disorders. J Clin Sleep Med. 2015;11(10):1187–98.

40. Suarez-Giron M, Bonsignore MR, Montserrat JM. New organisation for follow-up and assessment of treatment efficacy in sleep apnoea. Eur Respir Rev 2019; 28: 190059 .

41. Josep M. Montserrat Canal ,Monique Suárez-Giróna, Carlos Egead, Cristina Embid,Mónica Matute-Villacísa, Luis de Manuel Martíneze, Ángel Orteuf, Javier González-Cappag,María Tato Cerdeirasg y Olga MedianoSpanish Society of Pulmonology and Thoracic Surgery positioning on the use of telemedine in sleep-disordered breathing and mechanical ventilation . Arch Bronconeumol. 2020 .

42. Lankford A. Wireless CPAP Patient Monitoring: Accuracy Study. Telemed J E Health 2004; 10(2): 162-169. 31

43. Roberto Sabato, Valentina Di Lecce, Onofrio Resta, Giovanna Elisiana Carpagnano, Andrea Portacci, Pasquale Tondo, Donato Lacedonia, Maria Pia Foschino Barbaro Home vs inpatient CPAP titration costs in OSA patients from Southern Italy: the role of telemedicine European Respiratory Journal 2020 56: 4812.

44. Lloberes P, Durán-Cantolla J, Martínez-García MÁ, et al. Diagnosis and treatment of sleep apnea-hypopnea syndrome. Spanish Society of Pulmonology and Thoracic Surgery. Arch Bronconeumol 2011; 47: 143–156.

45. Samuel T Kuna , David Shuttleworth , Luqi Chi , Sharon Schutte-Rodin , Eliot Friedman , Hengyi Guo , Sandeep Dhand , Lin Yang , Jingsan Zhu , Scarlett L Bellamy , Kevin G Volpp , David A Asch Web-based access to positive airway pressure usage with or without an initial financial incentive improves treatment use in patients with obstructive sleep apnea. Sleep 2015; 38: 1229–1236.

46. Nurit Fox , A J Hirsch-Allen, Elizabeth Goodfellow, Joshua Wenner, John Fleetham, C Frank Ryan, Mila Kwiatkowska, Najib T Ayas The impact of a telemedicine monitoring system on positive airway pressure adherence in patients with obstructive sleep apnea: a randomized controlled trial. Sleep 2012; 35: 477–481.

47. Matthias Frasnelli , Florent Baty, Jolanda Niedermann , Martin H Brutsche , Otto D Schoch Effect of telemetric monitoring in the first 30 days of continuous positive airway pressure adaptation for obstructive sleep apnoea syndrome – a controlled pilot study. J Telemed Telecare 2016; 22: 209–214.

48. Hoet F, Libert W, Sanida C, et al. Telemonitoring in continuous positive airway pressure-treated patients improves delay to first intervention and early compliance: a randomized trial. Sleep Med 2017; 39: 77–83.

49. Hwang D, Chang JW, Benjafield AV, et al. Effects of telemedicine education and telemonitoring on continuous positive airway pressure adherence. The Tele-OSA Randomized Trial. Am J Respir Crit Care Med 2018; 197: 117–126.

50. Olivera P, Danese S, Jay N, Natoli G, Peyrin-Biroulet L. Big data in IBD: a look into the future. Nat. Rev. Gastroenterol. Hepatol. 2019; 16: 312–21.

51. Budhiraja R, Thomas R, Kim M, Redline S. The role of big data in the management of sleep-disordered breathing. Sleep Med. Clin. 2016; 11: 241–55.

52. Bailly S, Meyfroidt G, Timsit JF. What's new in ICU in 2050: big data and machine learning. Intensive Care Med. 2018; 44: 1524–7.

53. Jaiswal SJ, Topol EJ, Steinhubl SR. Digitising the way to better sleep health. Lancet 2019; 393: 639.

54. 16 Leypunskiy E, Kiciman E, Shah M, Walch OJ, Rzhetsky A, Dinner AR, Rust MJ. Geographically resolved rhythms in Twitter use reveal social pressures on daily activity patterns. Curr. Biol. 2018; 28: 3763–75.e5.

55. Malhotra A, Crocker ME, Willes L, Kelly C, Lynch S, Benjafield AV. Patient engagement using new technology to improve adherence to positive airway pressure therapy: a retrospective analysis. Chest 2018; 153: 843–50.

56. Liu D, Armitstead J, Benjafield A, Shao S, Malhotra A, Cistulli PA, Pepin JL, Woehrle H. Trajectories of emergent central sleep apnea during CPAP therapy. Chest 2017; 152: 751–60.

57. Nigam G, Pathak C, Riaz M. A systematic review on prevalence and risk factors associated with treatment-emergent central sleep apnea. Ann. Thorac. Med. 2016; 11: 202–10.

58. Watson NF. Health care savings: the economic value of diagnostic and therapeutic care for obstructive sleep apnea. J. Clin. Sleep Med. 2016; 12: 1075–7.

59. Sanyam K. Mahajan, Balbir Singh Verma, Sunil Sharma,Kunal Mahajan Prevalence and predictors of moderate to severe Obstructive Sleep Apnea in patients admietted with acute coronary syndrome. Indian Heart Journal December 2020.

60. Jean-Louis Pépin, Sébastien Bailly, Renaud Tamisier Big Data in sleep apnoea: Opportunities and challenges Respirology, 14 August 2019 .

61. Punjabi NM. The epidemiology of adult obstructive sleep apnea. Proc Am Thorac Soc 2008;5(2):136–43.

62. Ma Y, Peng L, Kou C, Hua S, Yuan H. Associations of overweight, obesity and related factors with sleep-related breathing disorders and snoring in adolescents: a cross-sectional survey. Int J Environ Res Public Health 2017;14(2):194.

63. Vera M. Lugo,Onintza Garmendia,Monique Suarez-Girón,Marta Torres,Francisco J. Vázquez-Polo,Miguel A. Negrín,Anabel Moraleda,Mariana Roman,Marta Puig,Concepcion Ruiz,Carlos Egea,Juan F. Masa,Ramon Farré,Josep M. Montserrat. Comprehensive management of obstructive sleep apnea by telemedicine: Clinical improvement and cost-effectiveness of a Virtual Sleep Unit. A randomized controlled trial. . Published: October 24, 2019 .

64. Atsushi Kara Protecting Privacy in Remote-Patient Monitoring . ComputerVolume 34Issue 5May 2001 pp 24–27 .

65. Heather Engleman, Christy Stitt, Lauren Creswick, Nuno Cachada, Matthew Thomas, Jonathan Leahy, Sarah M artin, Neena Derashri, Tom Kelly Effects on CPAP use of a patient support mobile app European Respiratory Journal 2018.

66. Monique Suarez-Giron, Onintza Garmendia, Vera Lugo, Concepción Ruiz, Neus Salord,Xavier Alsina, Ramón Farré, Josep M. Montserrat, and Marta Torres Mobile health application to support CPAP therapy in obstructive sleep apnoea: design, feasibility and perspectives ERJ Open Res. 2020 Jan; 6(1): 00220-2019.