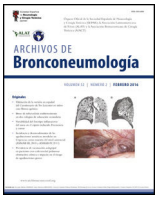
Arch Bronconeumol. 2020;56(11):689–690

Sociedad Española de Neumología y Cirugía Torácica SEPAR

ARCHIVOS DE Bronconeumología

www.archbronconeumol.org



Editorial

Cluster Analysis to Identify Apnea–Hypopnea Syndrome Phenotypes: Where Are We Heading?*

Análisis de clúster para identificar fenotipos de síndrome de apneas-hipopneas del sueño: ¿hacia dónde vamos?

Sleep apnea–hypopnea syndrome (SAHS) is a complex, heterogeneous, multifactorial disorder with a variable clinical presentation.[1] Continuous positive airway pressure (CPAP) treatment is effective in symptomatic patients. However, while there is strong evidence for the association between severe SAHS, cardiovascular disease (CVD), and mortality in observational studies, randomized clinical trials have shown that CPAP does not reduce the risk of these outcomes.[2] One possible explanation is that, at present, the management of the disease is based mainly on the apnea–hypopnea index (AHI), despite the fact that it is difficult for a single parameter to capture the entire heterogeneity of the disease. This situation underlines the need for precision medicine in SAHS. Just as phenotypes have been described in other chronic diseases such as asthma and COPD, attempts have been made in the last decade to identify SAHS phenotypes that can characterize patients with a higher risk of morbidity and mortality and a higher likelihood of responding to treatment. A series of statistical techniques have been used to analyze multifactorial data, one of the most important being cluster analysis, a multivariate statistical technique that seeks to group elements (or variables) in the attempt to achieve the maximum homogeneity within groups and the greatest difference between groups.[3]

The validity of the identification of phenotypes will depend on the homogeneity of the variables analyzed, their progress over time, and their reproducibility.

One of the first cluster analyses in SAHS was the Iceland Cohort (ISAC) conducted in 2014.[4] Since then, other studies have been published, many of which have focused on moderate-severe SAHS, although some include mild manifestations.[5–8] However these studies differ widely in terms of variables studied, cluster methods applied, and the duration of follow-up. Therefore, many different phenotypes have been identified and few have been associated with relevant clinical outcomes.

The ISAC study identified 3 phenotypes, classified as patients with "disturbed sleep" (32.7%), "minimally symptomatic" patients (24.7%) and patients with "excessive daytime sleepiness" (42.6%). One of the aims of this study was to determine if there was a higher likelihood of comorbidities (hypertension [HT], diabetes, CVD) in the "minimally symptomatic" group. Vavougios et al.[6] identified 6 groups, of which 2 had severe SAHS and 2 had moderate SAHS, differentiated by the presence of comorbidities. In patients with a similar AHI, the variables associated with "sick" phenotypes were age, body mass index (BMI), presence of HT, and lower daytime oxygen saturation. Similarly, Lacedonia et al.[9] identified a phenotype with more comorbidities that was associated with higher nocturnal and daytime hypoxemia and a higher BMI. Turino et al.,[10] in a cohort of patients receiving CPAP, found 2 phenotypes associated with higher mortality: the "neoplastic" group (with a high prevalence of malignant neoplasms) and "oldest (mean age 72 years) and cardiac disease patients".

Another limitation of most of these studies, apart from the variability of the parameters analyzed, is that their cross-sectional design rules out any prediction of progress of the phenotypes over time with respect to relevant clinical findings. The first study to analyze the clinical course of phenotypes was that of Zinchuk et al.[8]: this group identified 7 phenotypes according to 65 polysomnographic variables. The groups that were significantly associated with the primary outcome (a combination of stroke, transient ischemic attack, acute coronary syndrome, or death) at 4.9 years presented "restless leg syndrome", "hypopnea and hypoxia", and "combined severe". No association with AHI was identified. A second study of the original ISAC cohort described the 2-year follow-up of the original phenotypes in subjects treated with CPAP; improved symptoms were observed in all three groups. Although CPAP adherence and symptomatic improvement were greater in the group with excessive daytime sleepiness, there were no differences in the prevalence of comorbidities.[11]

ISAC is the only study that other cohorts have attempted to reproduce, but besides finding some differences in the number of clusters and their characteristics, the association with comorbidities of these studies also proved different:

- Kim et al.[12] identified 3 clusters similar to those described in ISAC: in this case, the "minimally symptomatic" group was the most prevalent and no phenotype was found to be associated with more comorbidities, except for a higher prevalence of HT in patients with "disturbed sleep". Unlike ISAC, the cohort was a general Korean population, and cultural differences may account

* Please cite this article as: Silveira MG, Lloberes P. Análisis de clúster para identificar fenotipos de síndrome de apneas-hipopneas del sueño: ¿hacia dónde vamos? Arch Bronconeumol. 2020;56:689–690.

for the different manifestation of symptoms and partly justify the different outcomes.

- Keenan et al.[13] reproduced ISAC in a new clinical cohort in Iceland and in another multi-ethnic cohort. They found 5 clusters (80% of patients were in the original 3 clusters) with similar prevalences to ISAC, but the "disturbed sleep" group was the one with the highest prevalence of comorbidities.
- The Sleep Heart Health Study cohort went a step further by following patients for up to 11.8 years and analyzing the incidence of CVD. In addition to the three ISAC groups, they identified a new group: "moderate sleepiness". In the "excessive daytime sleepiness" group (16.7%), a higher prevalence and incidence of CVD was observed, but surprisingly, the greater AHI score of this group is not discussed.[14]

The somewhat reproducible finding of the 3 clinical ISAC phenotypes in different cohorts is interesting. However, the phenotype most associated with comorbidities varies ("minimally symptomatic" in the original, "disturbed sleep" in the Kim et al.[12] study, none in Keenan et al.'s Iceland cohort[13]), prompting us to ask if they are really identifying the same phenotypes.

To date, cluster studies in SAHS reflect biases derived from variables previously established in the analysis. Thus, the generalization of the described phenotypes is limited by methodological differences, and further studies using a multifactorial approach (clinical, physiological, biological, polysomnographic parameters, clinical consequences) and a consensus definition of the variables analyzed will be needed to evaluate the most appropriate grouping techniques. Incorporating large quantities of data (big data) from electronic medical records is a promising strategy for advancing precision medicine in sleep apnea.

References

1. Ayas NT, Owens RL, Kheirandish-Gozal L. Update in Sleep Medicine 2014. Am J Respir Crit Care Med. 2015;192:415–20, http://dx.doi.org/10.1164/rccm.201503-0647UP.
2. Yu J, Zhou Z, McEvoy RD, Anderson CS, Rodgers A, Perkovic V, et al. Association of positive airway pressure with cardiovascular events and death in adults with sleep apnea: a systematic review and meta-analysis. JAMA. 2017;318:156–66, http://dx.doi.org/10.1001/jama.2017.7967.
3. Everitt BS, Landau S, Leese M, Stahl D. Cluster analysis. 5th ed. London: John Wiley & Sons, Ltd; 2011.
4. 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;44:1–8, http://dx.doi.org/10.1183/09031936.00032314.
5. Joosten SA, Hamza K, Sands S, Turton A, Berger P, Hamilton G. Phenotypes of patients with mild to moderate obstructive sleep apnoea as confirmed by cluster analysis. Respirology. 2012;17:99–107, http://dx.doi.org/10.1111/j.1440-1843.2011.02037.x.
6. Vavougios GD, Natsios G, Pastaka C, Zarogiannis SG, Gourgoulianis KI. Phenotypes of comorbidity in OSAS patients: combining categorical principal component analysis with cluster analysis. J Sleep Res. 2016;25:31–8, http://dx.doi.org/10.1111/jsr.12344.
7. Mihaicuta S, Udrescu M, Topirceanu A, Udrescu L. Network science meets respiratory medicine for OSAS phenotyping and severity prediction. PeerJ. 2017;5:e3289, http://dx.doi.org/10.7717/peerj.3289.
8. 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;73:472–80, http://dx.doi.org/10.1136/thoraxjnl-2017-210431.
9. Lacedonia D, Carpagnano GE, Sabato R, Storto MM, Io Palmiotti GA, Capozzi V, et al. Characterization of obstructive sleep apnea–hypopnea syndrome (OSA) population by means of cluster analysis. J Sleep Res. 2016;25:724–30, http://dx.doi.org/10.1111/jsr. 12429.
10. Turino C, Bertran S, Gavaldá R, Teixidó I, Woehrle H, Rué M, et al. Characterization of the CPAP-treated patient population in Catalonia. PLoS One. 2017;12:1–12, http://dx.doi.org/10.1371/journal.pone.0185191.
11. Pien GW, Ye L, Keenan BT, Maislin G, Björnsdóttir E, Arnardottir ES, et al. Changing faces of obstructive sleep apnea: treatment effects by cluster designation in the icelandic sleep apnea cohort. Sleep. 2018;41:1–13, http://dx.doi.org/10.1093/sleep/zsx201.
12. Kim J, Keenan BT, Lee SK, Pack AI, Lim DC, Shin C. Symptom-based subgroups of Koreans with obstructive sleep apnea. J Clin Sleep Med. 2018;14:437–43, http://dx.doi.org/10.5664/jcsm.6994.
13. Keenan BT, Kim J, Singh B, Bittencourt L, Chen NH, Cistulli PA, et al. Recognizable clinical subtypes of obstructive sleep apnea across international sleep centers: a cluster analysis. Sleep. 2018;41:1–14, http://dx.doi.org/10.1093/sleep/zsx214.
14. 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, http://dx.doi.org/10.1164/rccm.201808-1509OC.

María Guadalupe Silveira,[a,*] Patricia Lloberes[b]

[a] *Servicio de Neumología, Parc Sanitari Sant Joan de Déu, Sant Boi de Llobregat, Barcelona, Spain*

[b] *Servicio de Neumología, Hospital General Universitario Vall d'Hebron. Ciber Enfermedades Respiratorias (CIBERES), Barcelona, Spain*

* Corresponding author.
E-mail address: mgsilveira@gmail.com (M.G. Silveira).