Unsupervised Learning to Understand Patterns of Comorbidity in 633,330 Patients Diagnosed with Osteoarthritis

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Abstract: With the advent of big data in healthcare, machine learning has rapidly gained popularity due to its potential to analyse large volumes of complex data from a variety of sources. Unsupervised learning can be used to mine data and discover patterns such as sub-groups within large patient populations. However challenges with implementation in large-scale datasets and interpretability of solutions in a real-world context remain. This work presents an application of unsupervised clustering techniques for discovering patterns of comorbidities in a large dataset of osteoarthritis patients with a view to discover interpretable and clinically-meaningful patterns.

1 INTRODUCTION

Electronic health records present a wealth of routinely collected patient care information that can be used for data-driven health research (Binder and Blettner 2015), (Ehrenstein, Kharrazi et al. 2019).

Machine learning has shown potential for analysis of large volumes of complex, multi-modality health data, including pattern recognition to unravel sub-groups of patients within a large population (Cohen, Vawdrey et al. 2015, Pinedo-Villanueva, Khalid et al. 2018, Windgassen, Moss-Morris et al. 2018, Khalid and Prieto-Alhambra 2019, Agrawal and Prabakaran 2020). A variety of algorithms, clustering strategies, and evaluation criteria exist, as these choices are largely dataset- and application- dependent (Liao, Li et al. 2016, Grant, McCloskey et al. 2020).

In this paper we demonstrate the application of unsupervised learning methods for the task of identifying patterns of comorbidities within a large cohort of osteoarthritis and methods for evaluating an optimal clustering solution.

1.1 Clinical Context

Osteoarthritis (OA) is a musculoskeletal disorder that occurs when joint cartilage deteriorates, causing inflammation, stiffness, reduction of the mobility and pain on joins. The most commonly affected areas include knees, hands, hip and spine. OA is considered the most common type of arthritis and it is estimated to affect one of ten adults just in the UK (Swain, Sarmanova et al. 2020). Patients diagnosed with OA can experience considerable deterioration of their life quality and severe cases can require a joint replacement to reduce pain and restore joint function.

In addition to the personal and social implications of the disease, OA has an important economic impact. The National Joint Registry estimate that more than 90% of hip, knee and ankles replacements, and 59% of shoulder replacements in 2019 at the UK were caused by OA (NJR Report 2020). Moreover, patients with OA are more likely to have other comorbidities such as hypertension, dyslipidaemia and back pain (Swain, Sarmanova et al. 2020).

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The study of comorbidity patterns in OA patients at the time of OA diagnosis can help to identify sub-groups of patients e.g., individuals who might require additional care. This can in turn aid patient care decision-making and healthcare resource allocation.

1.2 Contribution in This Paper

Unsupervised machine learning methods such as cluster analysis are well-suited to the problem of patient sub-group identification (Pinedo-Villanueva, Khalid et al. 2018, Violan, Roso-Llorach et al. 2018, Grant, McCloskey et al. 2020, Hansen, Angquist et al. 2020, Wartelle, Mourad-Chehade et al. 2021).

In this work, we demonstrated the application of cluster analysis methods to a large routinely collected dataset representative of patients diagnosed with OA to unravel patterns of OA comorbidities.

Although cluster analysis methods are widely known, their use for detecting comorbidity patterns in a large and representative database of OA patients is presented for the first time in this work, and we describe key methodological challenges in implementing cluster analysis with a large sample size using an open-source software.

2 METHODS

2.1 SIDIAP Database

The Information System for Research in Primary Care (SIDIAP) is a healthcare database that contains de-identified patients records from more than 370 primary care teams in Catalonia (Spain), covering approximately 80% of the Catalan population (https://www.sidiap.org/).

2.2 Data

Participants aged ≥18 years with at least one physician-recorded diagnosis of OA for hip, knee, ankle/foot, wrist/hand, or site recorded as 'unspecified' from 1st of January 2006 to 31st of June 2020 in SIDIAP database were included in the study cohort. Incident cases i.e., first-ever diagnoses of OA cases were identified, and individuals were followed-up from the first diagnosis date (index date).

Patients with data recorded for less than a year before index date were excluded. Exclusion criteria also included any record of specific non-OA diagnosis (soft-tissue disorders, other bone/cartilage diseases) at the same joint in the 12 months before or after the recorded OA/joint pain consultation.

For the OA cohort, a total of 58 comorbidities of OA, identified by clinical experts and literature, were available in the dataset. Patient characteristics included socio-demographics, medical history, clinical procedures, laboratory tests, and treatments.

2.3 Pre-processing

Prevalence of the 58 OA comorbidities was measured. Comorbidities with less than 1% prevalence in the dataset were excluded. Highly correlated variables were identified using Pearson correlation: if a pair of comorbidities had a correlation coefficient > ±0.6, clinical expert opinion was used to consolidate the two comorbidities.

2.4 Cluster Analysis

Cluster analysis was used to split the dataset based on patterns of comorbidities and identify sub-groups of individuals with similar comorbidities.

The choice of clustering technique can be guided by the nature of data (e.g., categorical or continuous distribution) and the goal of the clustering task. Hard clustering may be preferred where it is desirable to assign each individual to a single group (non-overlapping clusters). Conversely, soft clusters generate cluster membership probabilities for each individual, such that an individual may have membership in more than one cluster (overlapping-clusters).

2.4.1 K-means

K-means is one the most popular hard clustering approaches, perhaps for being one of the simplest and less computational demanding. Ideally, it is meant for continuous data, but it can be applied to binary variables not highly correlated (Henry, Dymnicki et al. 2015).

In k-means we must pre-specify the desired number of clusters (k). Then, k randomly selected points from the d-dimensional space are assigned to be the cluster centroids (in our case, k random individuals became centroids). The distance between each individual and the centroids is computed, and each individual is assigned with its closest centroid. After that, clusters centroids are re-calculated based on the values within each group, and individuals are re-allocated to the new closest centroid. Re-calculation and re-allocation steps are repeated until position of cluster centroids stops changing.

Since k-means is sensitive to initial random selection of centroids, the obtained solution might become trapped in a local minimum. To prevent this

limitation, the algorithm should be repeated with random initialisation and the results pooled.

Cluster Evaluation in K-means

The choice of the optimal number of clusters ($\hat{k}$) can be subjective, but we can use a set of internal and external evaluation criteria to assist us in the decision. Additionally, both evaluations can provide us a better understanding of the performance of the cluster algorithm, and the existing grouping behaviour of the data.

The internal evaluation aims to find the solution of k clusters that maximizes the homogeneity of individuals within a cluster, while enhances the heterogeneity between different clusters. The simplest criteria to evaluate this is based on measuring the variance or scatter within a cluster: the within-cluster sum of squares (WCSS).

$$WCSS = \Sigma_{k=1}^{K}\Sigma_{i\in S_k}\Sigma_{j=1}^{d}(x_{ij} - \bar{x}_{ij})^2 \quad (1)$$

where S_k is the subset of individuals assigned in the k^{th} cluster, $\bar{x}$ represents the cluster mean, and k is the candidate number of clusters, k = 1:K. K is the maximum numbers of clusters considered. Other methods that are well described in the literature and are frequently used are Calinski-Harabasz (Caliński and Harabasz 1974), Gap (Tibshirani, Walther et al. 2001), and Silhouette (Rousseeuw 1987). The $\hat{k}$ is the k solution where all or most of the criteria concur, but when the results are not clear, the best is to select few models and assess them through an external and clinical evaluation.

The external evaluation uses independent variables (i.e., external, not included in the clusterization, but related to cluster features) to describe the cluster solutions, and therefore externally validating it. It can be especially useful when there is no clear consensus of $\hat{k}$ using the internal evaluation.

In our example, we have included age (< 50 years, between 50 and 70 years, and > 70 years), index of deprivation (rural areas, socioeconomic status > 3), and current smoking status.

2.4.2 Latent Class Analysis

Latent Class Analysis (LCA) is a type of soft clustering that explains the heterogeneity between individuals regarding a particular compilation of measured items. LCA is a finite mixture model: instead of measuring the distance between individuals, LCA uses a mix of distributions to determine the most likely model that describes the heterogeneity of the data as a finite number of groups (latent classes) (figure 1). In other words, it produces an estimate of how likely is for an individual to belong to a cluster by summarizing their patterns of characteristics into a pre-specified number of latent classes.

In fact, the larger number of features involved in the analysis, the higher number of patterns can be found in the data (the increment is exponential), which increases the difficulty of the results interpretation. But LCA can reduce the total number of possible patterns by compressing them into subsets, showing us the most prevalent of them at the cost of losing certain amount of specificity. Nonetheless, the provided patterns will be more comprehensible and practical while still parsimonious.

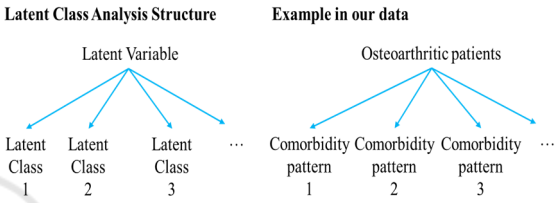


Figure 1: Structure of latent class analysis and application in our data. A latent variable can be represented by latent classes (i.e., groups/subgroups of the latent variable that cannot be measured). In our example, we want to represent patients with osteoarthritis into groups according to their combination of comorbidities (i.e., patterns).

LCA was originally designed for discrete variables, which is the case of the assessed variables presented in this work, but there is an extension for dealing with longitudinal data (Jung and Wickrama 2008). As with k-means, LCA requires the introduction of the expected number of k classes, but in this case we can statistically determine the performance of the proposed models in representing the studied population.

Cluster Evaluation in Latent Class Analysis

The $\hat{k}$ in LCA is obtained by comparing the performance of the models from k = 1 or 2, to a reasonable number of subgroups. For example, we will analyse up to k = 10. We can calculate different criteria methods to compare the models, such as the likelihood and its logarithm, the entropy, entropy R^2, the Akaike's Information Criteria (AIC), Bozdogan's Criterion (CAIC), the Bayesian Information Criteria (BIC, as well known as Schwartz's Bayesian Criterion) and the Akaike's Bayesian information criterion (ABIC).

In this paper, we have used the entropy R2, the ABIC, BIC, CAIC criteria methods and log-likelihood ratio.

Entropy in cluster analysis explains the amount of disorder (dispersion) in the data, and points how good the prediction of the cluster membership can be. The score ranges from 0 to 1, where low values represent less different characteristics/patterns; and high numbers represent greater disorder, where is more likely for the model to be distributed correctly across different groups. A common desired threshold to set a good entropy is > 0.7. Boeschoten et al. (2017) fully report the methodology to calculate the entropy R^2 in LCA models (Boeschoten, Oberski et al. 2017).

The AIC criteria measures of the goodness of fit of the proposed model derived from frequentist probability (Akaike 1987), while BIC is derived from Bayesian probability (Schwarz 1978). Compared to BIC, complex models are less penalized in AIC. The CAIC is an extension of the AIC procedure with a stronger penalty for overparametrized models (Bozdogan 1987), and ABIC is a sample-sized adjusted BIC (Sclove 1987). In all these parameters, the lowest value reflects the best model. In mixed models, we can measure these parameters as follows:

$$AIC = -2\Lambda + 2\Phi \quad (2)$$

$$CAIC = 2\Lambda + \Phi(1 + lnN) \quad (3)$$

$$BIC = -2\Lambda + \Phi \ln N \quad (4)$$

$$ABIC = -2\Lambda + \ln\left(\frac{N+2}{24}\right) \quad (5)$$

Where Λ is the maximum log-likelihood and Φ is the total number of estimated parameters (degrees of freedom) of the model, and N is the number of participants in the subset.

Ideally, the optimal LCA model will be the one with the lowest value obtained in CAIC, BIC and ABIC criteria, and the highest entropy R^2, but it might happen that criteria values keep decreasing and entropy increasing. Like the strategy of selecting the $\hat{k}$ in K-means, we choose few models for a manual evaluation to unravel the underlying patterns of comorbidities from each cluster by observing the posterior probabilities (i.e., probability from patients to be allocated to one cluster).

2.5 Software Used

All the analysis were conducted using R 4.1.1 for Windows.

3 RESULTS

We identified 633,330 patients diagnosed with OA in SIDIAP database, and from the total 58 comorbidities, only 36 were present in more than 1% of the population (Table 1). No correlations equal or above 0.6 were found.

Table 1: Prevalence of OA patients' comorbidities. In bold: comorbidities excluded in the analysis (<1.0% of prevalence). Abbreviations: BHP, benign prostate hypertrophy; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; IBD, inflammatory bowel disease; PVD, peripheral vascular disease; SLE, Systemic lupus erythematosus.

Comorbidities (total = 58)	
N=633330	
Anaemia	48281 (7.62%)
Ankylosing spondylitis	**550 (0.09%)**
Anxiety	80554 (12.7%)
Arrythmia	32605 (5.15%)
Asthma	15960 (2.52%)
Autism	**24 (0.00%)**
Back/neck pain	212986 (33.6%)
BHP	33560 (5.30%)
Cateract	**0 (0%)**
Chronic heart disease	34300 (5.42%)
Chronic heart failure	15850 (2.50%)
Sinusitis	**2675 (0.42%)**
Chronic Kidney disease	36098 (5.70%)
COPD	23961 (3.78%)
Vitamin D deficiency	7569 (1.20%)
Dementia	12467 (1.97%)
Depression	48757 (7.70%)
Diabetes	57498 (9.08%)
Hyperlipidemia	11602 (1.83%)
Eczema	21924 (3.46%)
Epilepsy	**2671 (0.42%)**
Fatigue	16852 (2.66%)
Fibromyalgia	10008 (1.58%)
Gall bladder stone	21346 (3.37%)
GERD	6474 (1.02%)
Gout	12388 (1.96%)
Hearing impairment	41563 (6.56%)
Hepatitis	**455 (0.07%)**
Hypothyroidism	22153 (3.50%)
HIV/AIDs	**252 (0.04%)**
Hypertension	149092 (23.5%)
Hyperthyroidism	**4789 (0.76%)**
IBD	14810 (2.34%)
Insomnia	44278 (6.99%)
Irritable bowel syndrome	**4520 (0.71%)**
Leukaemia	**915 (0.14%)**
Liver	**2336 (0.37%)**
Lymphoma	**948 (0.15%)**
Migrane	10401 (1.64%)
Multiple sclerosis	**248 (0.04%)**
Obesity	80387 (12.7%)
Osteoporosis	45261 (7.15%)
Other vessel diseases	9621 (1.52%)

Table 1: Prevalence of OA patients' comorbidities. In bold: comorbidities excluded in the analysis (<1.0% of prevalence). Abbreviations: BHP, benign prostate hypertrophy; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; IBD, inflammatory bowel disease; PVD, peripheral vascular disease; SLE, Systemic lupus erythematosus (cont).

Parkinson	**3872 (0.61%)**
PVD	**2773 (0.44%)**
Polymyagia rheumatica	**3408 (0.54%)**
Psoriasis	8179 (1.29%)
Psoriatic arthritis	580 (0.09%)
Rheumatoid arthritis	**3250 (0.51%)**
Schizophrenia	**985 (0.16%)**
Allergy	80449 (12.7%)
Sjogen's syndrome	**2070 (0.33%)**
SLE	**504 (0.08%)**
Solid malignancy	23946 (3.78%)
Stroke	20986 (3.31%)
Substance abuse	40423 (6.38%)
Thrombotic diseases	**823 (0.13%)**
Tuberculosis	**1321 (0.21%)**

3.1 Internal Evaluation

Figure 2 shows the results for internal validation of k-means using WCSS, and figure 3 for LCA using Entropy R^2, goodness of fit tests and likelihood values. Other metrics (e.g., Gap, Silhouette and Calinski-Harabasz) were unable to converge given the sample size. Running times for LCA were larger, especially for higher numbers of k (up to three weeks when k = 10 in LCA vs. one day in K-means). WCSS did not change by more than ±1 std after k=6, and similar effect was observed in curves from internal validation of LCA analysis. Therefore, to determine an optimal number of clusters, cluster visualisation was performed for k=4, 5, and 6 in both methods.

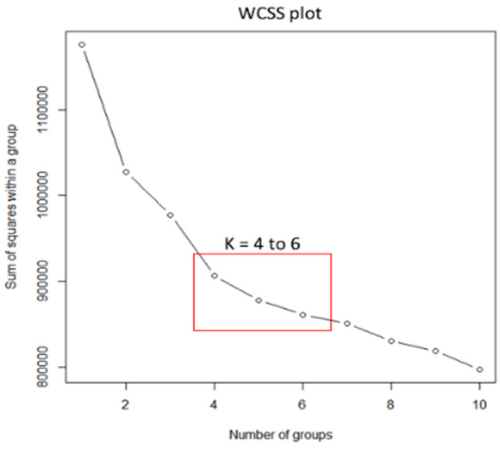


Figure 2: Representation of the Within-Cluster-Sum-of-Squares (WCSS) for each number of k.

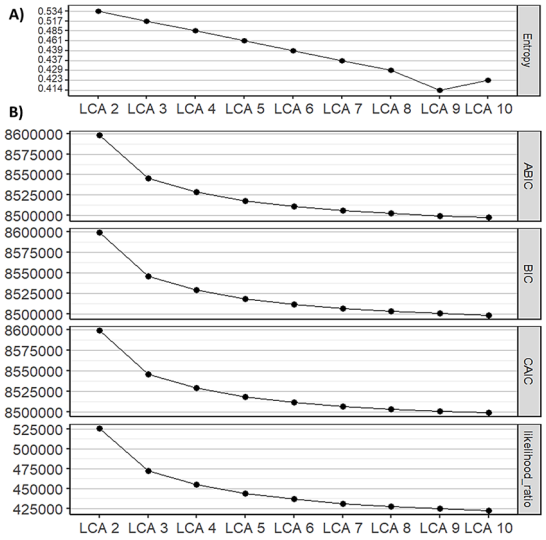


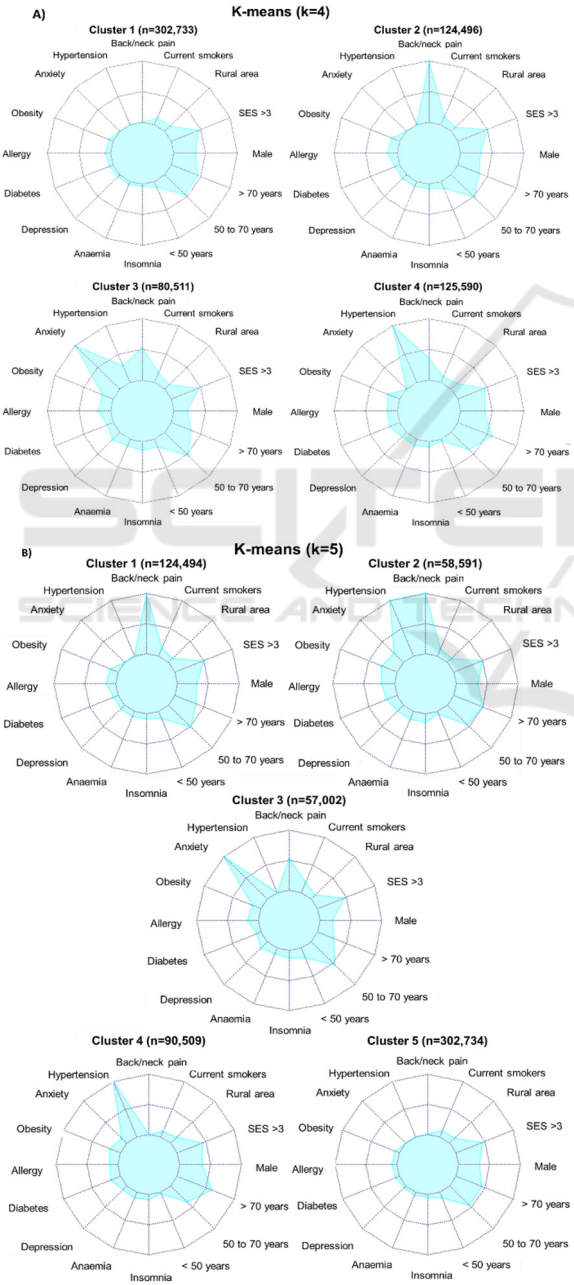
Figure 3: Representation of A) entropy R^2 values and, B) goodness of fit tests and likelihood ratio for each LCA when k ranges from 1 to 10.

When using k = 4, k-means (figure 4A) show a generally healthy cluster, a back/neck pain cluster, an anxiety cluster with half of the patients experiencing back/neck pain, and a hypertension cluster with around forty percent of patients experiencing back/neck pain. In LCA (figure 5A), first 2 clusters present the same main comorbidities: relatively healthy group and back/neck pain. Back/neck pain cluster is also linked with mental disorders (anxiety and depression), migraine, insomnia, and/or other pain conditions (fatigue and fibromyalgia). Third and fourth clusters present a main prevalence of hypertension and back/neck pain. However, third cluster is linked to more comorbidities, including mental disorders, insomnia, anaemia, diabetes, and/or set of different cardiovascular disorders (arrythmia, stroke, chronic heart disease and chronic heart failure), among others.

When using k = 5, k-means (figure 4B) distinguish patients in back/neck pain, back/neck pain plus hypertension, anxiety with half of them experiencing back/neck pain, hypertension, and healthy clusters. LCA (figure 5B) distinguish patients among hypertension and back/neck pain plus many other comorbidities; hypertension and back/neck pain, but less presence of other comorbidities; back/neck pain, combined with mental disorders and/or allergy; hypertension; and healthy clusters.

When using k = 6, k-means (figure 4C) stratify patients into back/neck pain, healthy, anxiety, obesity, hypertension and back/neck pain, and hypertension clusters. LCA results (figure 5C) show: a cluster with prevalence of hypertension followed by

back/neck pain, obesity and diabetes; second cluster with hypertension followed by back/neck pain, plus different cardiovascular disorders, anaemia and/or diabetes; third cluster with back/neck pain followed by hypertension, plus allergy, mental disorders and/or obesity; forth cluster with back/neck pain and low presence of other comorbidities; fifth cluster with hypertension followed by back/neck pain, and low occurrence of other comorbidities; and last, a generally healthy cluster.



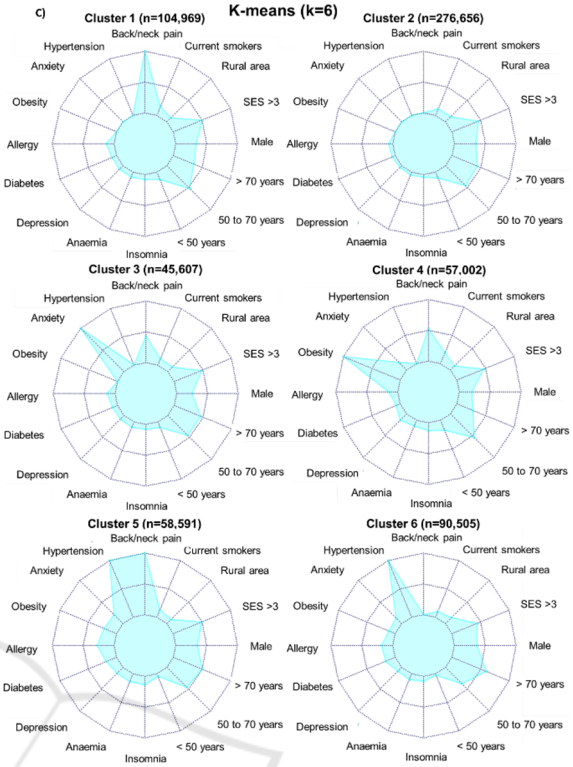


Figure 4: Distribution of comorbidity patterns within a cluster using K-means: A) k = 4, B) k = 5, and C) k=6. Number of patients in each cluster is described. External variables not included in the cluster algorithm: smoke, rural area, SES, male and age groups. Abbreviations: SES, urban socioeconomic status where >3 are more deprived areas.

3.2 External Evaluation

In k-means graphs, we included the external features along with the 10 most prevalent comorbidities (figure 4). In k = 4, clusters 1 and 4 are older patients. These clusters were annoted as healthy and hypertension groups, respectively. Cluster 3, the anxiety group, has the lower proportion of men. When k = 5, cluster 4 had the oldest population, followed by cluster 5 and 2 (identified as hypertension, healthy and hypertension plus back/neck pain, respectively). Cluster 3, once again anxiety group, had the lowest proportion of males. When k = 6, clusters 3 and 4 (anxiety and obesity, respectively) had lower male patients, and clusters 1 and 4 (back/neck pain and obesity, respectively) tend to have younger patients.

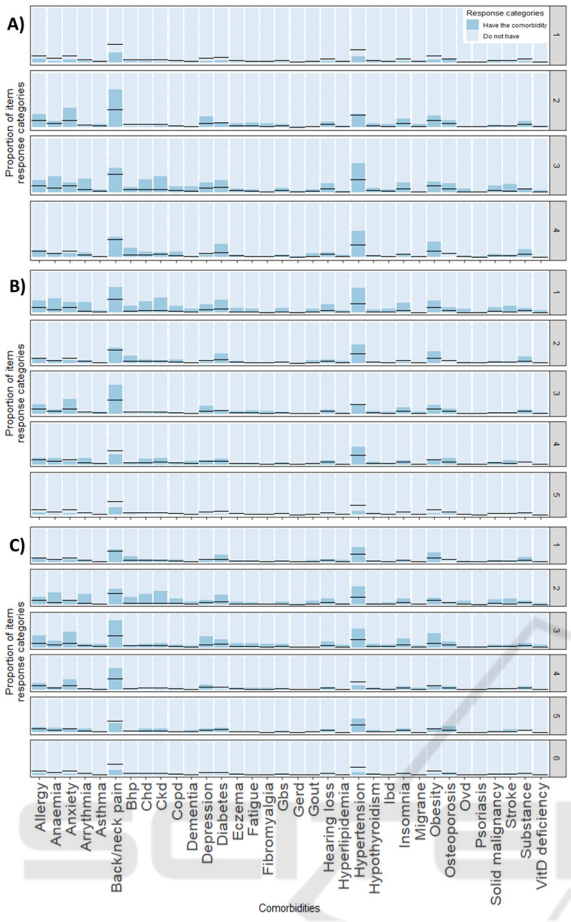


Figure 5: Distribution of comorbidity patterns within a cluster using LCA: A) k = 4, B) k = 5, and C) k=6. Black horizontal lines represent the prevalence of the comorbidity before the clusterization. Abbreviations: Bhp, benign prostate hypertrophy; Chd, chronic heart disease; Ckd, chronic kidney disease; Copd, chronic obstructive pulmonary disease; Gbs, gall bladder stone; Gerd, gastroesophageal reflux disease; Ibd, inflammatory bowel disease; Ovd, other vessel diseases; Substance, substance abuse.

4 DISCUSSION

Cluster analysis is a type of unsupervised learning methods and therefore, we cannot test in absolute terms whether the number of groups and the obtained grouping is accurate or the most optimal. The general practice is to include more than one method and to compare the subsequent solutions.

In terms of the limitations of each cluster method, we have observed that large datasets imply difficulties in calculating the internal validation methods based on distance matrix in K-means, and larger running times in LCA. In terms of interpretability, results from k-means are easier to interpret than LCA. Distinct clusters are assigned to patients, and therefore, highly distinguishable groups are created. Despite this, soft classification by LCA allows us to detect more complex patterns that possibly represents better the behaviour and interaction of comorbidities among the OA patients.

Comparing the composition of the different clusters across both methods, similar clusters can be found: a healthy group, patients with high prevalence of back/neck pain and hypertension (alone or combined), mental disorders (i.e., anxiety and/or depression), etc. Observing the evolution of clusters when incrementing the k, higher number of groups in k-means seems to enhance patients' differences. But in LCA, clustering patients in 6 different groups obscures the interpretability rather than show more hidden patterns. In this method, our proposed optimum number of stratification is 5, where we can distinguish a cluster of patients with high complex comorbidities profiles (cluster 1: hypertension and back/neck pain plus many other comorbidities) from a cluster of patients with hypertension and back/neck pain but less prevalence of other complications (cluster 2), and from patients with not only back/neck pain but also mental disorders (cluster 3). Simultaneous comorbidities exacerbate pain and diminish the physical function (Calders and Van Ginckel 2018). Differentiation of individuals from cluster 1 and 2 leaded us to identify a sub-group of patients that potentially require further supervision. To confirm that, next steps will include an evaluation of the obtained clusters with an external outcome such as 10-years death or a change in a quality of life index.

Another limitation to note is that this work included all OA patients regardless of site. The location of the affected joint (e.g., OA in knee or hip) might have a different impact in the clinical profile of OA patients (and therefore their respective comorbidity patterns). Thus, examination of site-specific OA cohorts, such as knee OA, is part of the on ongoing work.

5 CONCLUSIONS

In this work, patterns of co-morbidities within a large OA population were examined and sub-groups identified. We have shown some of the challenges and strategies of unsupervised machine learning applied to a large dataset from a representative primary care database, including lack of convergence of several methods in K-means and the alternatives to

overcome it, large running times in LCA, and the complexity of interpreting the results.

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DISCLAIMER

This paper presents independent research funded by the Foundation for Research in Rheumatology (FOREUM) that currently is ongoing. Views expressed are those of the author(s) and not necessary those of all partners involved in FOREUM study.

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