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ABSTRACT

Objectives We aimed to delineate phenotypes in hand osteoarthritis (HOA) based on cardinal symptoms (pain, functional limitation, stiffness, aesthetic discomfort).

Methods: With data from the DIGItal COhort Design (DIGICOD), we performed hierarchical agglomerative clustering analysis based on Australian/Canadian HOA index sub-scores (AUSCAN) for pain, physical function, stiffness, and visual analogue scale for aesthetic discomfort. Kruskal-Wallis and Post-Hoc analyses were used to assess differences between clusters.

Results: Among 389 patients, we identified five clusters: cluster 1 (N=88) and cluster 2 (N=91) featured low and mild symptoms; cluster 3 (N=80) isolated aesthetic discomfort; cluster 4 (N=42) a high level of pain, stiffness, and functional limitation; and cluster 5 (N=88) the same features as cluster 4 but with high aesthetic discomfort. For clusters 4 and 5, AUSCAN pain was > 41/100 representing only one-third of our patients. Aesthetic discomfort (clusters 3 and 5) was significantly associated with erosive HOA and a higher number of nodes. The highly symptomatic cluster 5 was associated but not significantly with metabolic syndrome, and body mass index and C-reactive protein level did not differ among clusters. Symptom intensity was significantly associated with joint destruction as well as with physical and psychological burden. Patients' main expectations differed among clusters, and function improvement was the most frequent expectation overall.

Conclusions: The identification of distinct clinical clusters based on HOA cardinal symptoms suggests previously undescribed subtypes of this condition warranting further study of biological characteristics of such clusters and opening a path toward phenotype-based personalized medicine in HOA.

Significance and Innovation

- Symptoms management is the primary goal of hand osteoarthritis care and there is a critical need for better delineation.
- This study identified 5 clusters in hand osteoarthritis based on symptoms (pain, stiffness, physical function, and aesthetic discomfort) identifying very distinct patient's profiles.
- Our results could help investigators design future clinical trials, leading toward symptomatic phenotype-based personalized care in hand osteoarthritis.

INTRODUCTION

Osteoarthritis (OA) is the most frequent joint disease and a leading cause of pain and disability worldwide (1). The most common localization of OA is the hand, with an estimated prevalence of 8% and a lifetime risk of 39% for symptomatic hand OA (HOA) (2). HOA is classified by the American College of Rheumatology (ACR) criteria according to the clinical features of hand pain, aching or stiffness associated with hard-tissue enlargement of the distal interphalangeal, proximal interphalangeal, and/or first trapeziometacarpal joints, with some involvement of metacarpophalangeal joints (3). HOA is also characterized by typical radiographic hallmarks (joint space narrowing, osteophyte formation and bone remodeling, and malignment) (4).

HOA is a heterogeneous disease considering its risk factors such as sex, obesity, diabetes, or HOA family history (5) but also because of its distinct clinical presentation based on radiographic features (4,6). Likewise, we usually separate first carpometacarpal joint OA (i.e., rhizarthrosis) and nodal OA (7) and also non-erosive and erosive HOA (8). Nonetheless, the clinical assessment of patients with HOA indicates that HOA is also heterogeneous in terms of symptoms assessed by patient-related outcomes (PROs).

HOA symptoms are joint pain, functional limitation and stiffness leading to impairment in everyday life activities. The aesthetic discomfort of HOA has also been emphasized as an underestimated symptom (9). The variability of intensity of symptoms is wide, ranging from asymptomatic to highly symptomatic. So far, this heterogeneity is poorly studied and is not considered in current HOA phenotypes. However, recommendations for HOA management are driven by these symptoms (10). Despite their importance for diagnosis, assessment and therapeutic

management and their evident heterogeneity, HOA symptoms remain understudied. Thus, a better description of HOA symptoms and their associated features could lead to improved disease monitoring and therapeutic strategies.

The main objective of our study was to delineate the main clinical symptomatic phenotypes of HOA patients by using integrative analysis methods such as hierarchical clustering analysis based on the cardinal symptoms (i.e., pain, functional limitation, morning stiffness, aesthetic discomfort) reported by patients with HOA. Secondary objectives were to compare the clinical, radiographic, and biological features of the so-delineated clinical clusters.

PATIENTS AND METHODS

The DIGICOD cohort

The DIGItal COhort Design (DIGICOD) is a monocentric French university hospital-based prospective cohort of patients with symptomatic HOA (ClinicalTrials.gov: NCT01831570) (11) . Patients were included between April 2013 and June 2017. HOA patients underwent a clinical assessment of the hand, a general examination, blood sampling and hand radiography at baseline. Hand radiographs were scored by Kellgren-Lawrence (KL) grade (12) and the anatomical Verbruggen-Veys score (13). The present study involves the database for the baseline visit and has been reported according to the STROBE checklist for observational cohorts (https://www.strobe-statement.org/).

Inclusion and exclusion criteria

The inclusion criteria were age ≥ 35 years, a diagnosis of symptomatic HOA according to the ACR criteria (3) and one of the following: (i) ≥ 2 symptomatic joints among proximal or distal interphalangeal joints, (ii) radiographic KL grade ≥ 2 for the first interphalangeal joint, (iii) radiographic KL grade ≥ 2 for symptomatic thumb-base OA. The study was proposed to patients in a center specialized in HOA in the rheumatology department of Saint-Antoine hospital and in other hospitals of the Assistance Publique–Hôpitaux de Paris (AP–HP) but also from private practice, public conferences, and media advertisements. Patients were required to be part of the French social security system and to be able to understand and complete the different surveys in French. There was no pain or other symptom threshold for inclusion.

The main exclusion criteria were inflammatory destructive arthritis (rheumatoid arthritis or psoriatic arthritis), hand crystal-induced arthropathies, secondary HOA related to infection, trauma or rare genetic disorder, pregnancy and breastfeeding, and patient under protective measure or unable to express their consent. All participants provided their written informed consent before entering the cohort. The trial obtained all the regulatory and ethics validation from the local regulatory committee (Comité de Protection des Personnes, Paris Île-de-France IV). Patients and the public were involved in the reporting of the study, ensured by communications through patient's associations and dedicated general articles to the public.

Variable selection

For identifying clinical phenotypes, we focused on clinical variables related to the four cardinal symptoms in HOA that are assessed using PROs: pain, physical function, stiffness, and aesthetic discomfort. Pain, physical function, and stiffness intensity were assessed by using the sub-scores of the Australian/Canadian HOA index (AUSCAN) VA3.0 self-administered questionnaire (14). Each sub-score was normalized to a 0-100 scale. A physician assessed aesthetic discomfort with a single question "How high do you consider the aesthetic impact of your HOA?" on a visual analogue scale (VAS) from 0 to 100 mm (15).

To further characterise and investigate differences between phenotypes, we studied 19 clinical, radiographical and routine biological variables available in the DIGICOD case report form including: demographic criteria such as age and sex, HOA duration, (duration of OA referred to HOA symptomatic period and did not include the preclinical phase), family history of HOA, body mass index (BMI). We also included the presence or the absence of metabolic syndrome according to the Adult Treatment Panel (ATP) III criteria (16), C-reactive protein (CRP) level was collected and considered elevated if $\geq$ 5 mg/L. We quantified grip strength on the dominant hand measured 3 times by using a Jamar hydraulic hand dynamometer, recording the higher result from the 3 testing results recorded(17). Thumb base pain was defined as the presence of spontaneous pain in one of the two first carpometacarpal joint. The number of painful digital joints at palpation, digital nodes and digital joints with soft tissue swelling, were assessed in a range between 0 and 30 during a clinical examination performed by a rheumatologist in a department with HOA expertise. KL sum score for hands (18) (0–128), the presence or absence of. erosive HOA defined as "E" (erosion) or "R" (remodelling) phases for the Verbruggen-Veys score (13) in $\geq$ 2 joints were

measured and defined by an experimented radiologist. Patient's main expectation regarding HOA among pain, function, and aesthetic discomfort (only one choice possible) the Hospital Anxiety and Depression Scale (HADS) (19) was evaluated. Finally, we evaluated patients ongoing analgesic consumption, with paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and weak opioids defined as the intake of either codeine, dihydrocodeine or tramadol.

Statistical analysis

Non-supervised hierarchical agglomerative clustering analysis involved using the Ward's linkage method and the squared Euclidean distance. Clusters similarity and overlapping was controlled with a dimension reduction method based on multi-dimensional scaling (**Figure S1**).The optimal number of clusters was determined and confirmed by a combination of statistical criteria such as measurement of the within-cluster sum of square (WSS) and the gap statistic method (20,21) **(Figure S2, S3)** Hierarchical clustering is a deterministic algorithm and therefore reproducible. The stability of clustering partition was assessed with a non-parametric resampling method with two hundred bootstraps samples, cluster wise Jaccard index dispersion was calculated (22) (**Figure S4**). Finally, significance of our clustering was assessed with Gaussian Null Hypothesis Test as proposed with a Family Wise Error Rate (FWER) < 0.05 (23). Clustering analysis was performed with no imputation on missing values. Quantitative variables were analysed with a non-parametric Kruskal-Wallis test. The significance threshold was set at $p<0.05$ for statistical analysis. A Holm-Bonferroni method was applied on adjusted p-values for correction, to ensure the robustness of our results and limit bias associated to the multiplicity of statistical tests.

The features comparing clusters were analysed using as a reference the pauci-symptomatic cluster 1 with the Mann-Whitney-Wilcoxon test and Pearson Chi-squared test for quantitative and categorical variables, respectively. All analyses involved using R (R Core Team, 2013. R Foundation for Statistical Computing, Vienna, Austria. http://www.R-project.org/).

RESULTS

Description of the population

Among the 436 patients with HOA included at baseline, data for 10 were not analysed because of withdrawal of consent (N=1), unavailable hand radiographs (N=3) and not meeting inclusion criteria (N=6). Among the 426 patients, 37 were excluded for missing values regarding the AUSCAN pain, stiffness, and physical function sub-scores and the VAS score for aesthetic discomfort **(Figure 1)**. The mean ± SD age of the cohort was 66·5±7·4 years, 84% (n=329) of the cohort were women, the mean BMI was 25·1±4·4 kg/m^2, and erosive HOA was present in 134 (34·4%) patients .

Identification of 5 clusters of patients based on cardinal HOA symptoms

For the 389 patients analysed, hierarchical agglomerative clustering allowed for identifying 5 distinct clusters including 88, 91, 80, 42 and 88 patients for clusters 1 to 5, respectively **(Figure 2)**. Each cluster was homogeneous and distinct from each other in terms of symptom presentation. The composition of clusters is described in **Figure 3** and **Table 1**. Clusters 1 and 2 had low scores for all symptoms. Cluster 1 (N=88) consisted of very low symptomatic patients and cluster 2 (N=91) patients with mild symptoms and with a slight predominance of functional impairment. Clusters 3, 4 and 5 had high scores for one or multiple symptoms. Cluster 3 (N=80) consisted of

patients with isolated aesthetic discomfort and with a high VAS aesthetic score (mean [SD] 73·7 [20·2]) and low stiffness, pain, and function scores. Cluster 4 (N=42) patients presented high pain, stiffness, and function sub-scores but without aesthetic discomfort. Finally, the highest symptomatic cluster, cluster 5 (N=88), combined the features of the highly symptomatic cluster 4 with elevated aesthetic discomfort. We performed a descriptive analysis and comparison of the different clusters, and the main messages are presented below **(Table 2, Table S1, Figure S1)**.

Pain score was > 41/100 in one third of patients

The overall mean AUSCAN pain score was low, 25·8 (21·4)/100, and only patients in clusters 4 and 5 (N=122/389) had a mean AUSCAN pain score > 41. The number of painful joints upon palpation significantly differed among the clusters. Accordingly, the mean number of painful joints upon palpation was higher in clusters 4 and 5 than in the low symptomatic cluster 1 (7·2 [6·0] and 6·7 [4·9] vs 2·6 [3·4]). If the consumption of oral analgesics did not significantly differ between clusters, patients in cluster 4 and 5 presented a higher intake of weak opioids respectively (N = (15%) and N = (14.7 %) compared to cluster 1 (3.44 %).

Association of symptom intensity, joint destruction, and sex

The KL sum score for both hands significantly differed among clusters. The reference cluster 1 presented the lowest structural severity based on the KL sum score (mean 37·9/128 [17·5]) as compared with both highly symptomatic clusters 4 and 5 (48·9/128 [16·0], and 54·6/128 [14·3]) and as compared with the aesthetic-only cluster 3 (48·0/128 [17·2]).

Similarly, the male/female proportions significantly differed among the groups. The proportion of women was higher in the symptomatic clusters 3, 4, and 5 than cluster 1, with (N=74/80, 92·5%)

in cluster 3, (N=37/42, 88·1%) in cluster 4 and (N=84/88, 95·5%) in cluster 5 as compared with cluster 1 (N=62/88, 70·5%). HOA duration and age also differed among the clusters. Mean HOA duration was higher in cluster 2 (12·7 [9·7] years), cluster 3 (13·6 [9·5]), cluster 4 (14·0 [9·4] years) and cluster 5 (16·9 [10·8] years) than cluster 1 (8·3 [6·6]). Patients were older in clusters 4 and 5 than cluster 1 (mean age 68·3 [7·3], 68·6 [6·4], 64·9 [9·0] years).

Aesthetic discomfort was associated with erosive HOA and nodes

The proportion of patients with erosive HOA significantly differed among the clusters and was overrepresented in clusters with high aesthetic discomfort, whereas in cluster 1, 19/88 (21·6%) patients had erosive HOA patients. Indeed, although the number of patients with erosive HOA was 19/88 (21·6%) in cluster 1, it was 31/80 (38·8%) in cluster 3 (i.e., aesthetic only cluster) and N=43/88 (48·9%) in the highly symptomatic cluster 5 (p=0·0003). The number of nodes also significantly differed among the clusters. Aesthetic discomfort was associated with a higher number of digital joint nodes in cluster 3 (mean 13·1/30 [6·8]) and cluster 5 (14·8/30 [7·8]) than cluster 1 (10·1/30 [6·8]).

Highly symptomatic cluster associated with metabolic syndrome

Metabolic syndrome did not significantly differ among the clusters but the number of patients with metabolic syndrome was higher in the highly symptomatic cluster 5 than in the low symptomatic cluster 1 (N=40/88, 45·4%, vs N=23/88, 26·1%, p=0·013). Although the overall mean number of swollen joints was low in our cohort (1·1/30 [2·1]), it significantly differed among clusters and patients in the highly symptomatic cluster 5 with aesthetic discomfort had a higher number of swollen joints than those in cluster 1 (1·7/30 [1·8] vs 0·8/30 [1·8]). Of note, the clusters did not

differ significantly in BMI or CRP level. The number of patients with elevated CRP level was higher but not significantly in cluster 5 than in cluster 1 (N=11/88, 12·5%, vs N=4/88, 4·5%).

Function impairment was associated with thumb base pain

The proportion of patients with thumb base pain significantly differed among the cluster and was over-represented in cluster presenting function impairment. Cluster 2 characterized by isolated mild function impairment, presented higher thumb base pain compared to cluster 1 (N = 28 (30·8%) vs N = 12 (13·6%), p = 0·019). Similarly, cluster 4 and cluster 5 presented a higher proportion of thumb base pain compared to cluster 1 (N = 10 (23.8 %) p = 0.23, N = 26 (29.5 p = 0.017).

Symptom intensity was associated with physical and psychological burden

Grip strength of the dominant hand significantly differed among the clusters with a decrease in strength for patients with high symptom intensity in clusters 3, 4, and 5. The mean grip strength in cluster 1 was 31·8 [14·8] kg, which was higher than in the other symptomatic clusters (cluster 3: 24·0 [9·3] kg , cluster 4: 21·9 [10·6] kg and cluster 5: 21·8 [11·7] kg).

Similarly, anxiety and depression measured by the HADS significantly differed among the clusters and was higher in clusters 4 and 5 than cluster 1. The mean HADS score was 10·7 (5·3) for cluster 1 and 14·0 (6·5) and 15·0 (6·6) for clusters 4 and 5.

Patients' overall main expectation was physical function

We asked patients about their main expectation for treatment, with a unique answer among aesthetic, physical function, and pain. Patients' main expectations significantly differed among

clusters. Function was the overall main expectation in all clusters except in the highly symptomatic cluster 5, for which it was pain relief. Although in cluster 3, the leading complaint was aesthetic discomfort, aesthetics was not the main expectation for treatment because it involved 18/80 (22·5%) patients, whereas function and pain involved 32/80 (40%) and 30/80 (37·5%) patients, respectively.

DISCUSSION

We have proposed a computational approach to delineate the heterogeneity of HOA based on self-reported symptoms and the hierarchical clustering method. We identified 5 distinct clinical clusters based on the four cardinal HOA symptoms: pain, physical function, stiffness, and aesthetic discomfort. The wide variability in the intensity of these symptoms based on a simple PRO self-assessment allowed for determining 5 groups of patients: two low and mild symptomatic clusters; a cluster with isolated aesthetic discomfort; a cluster with high physical function, pain, and stiffness scores; and finally, a group of patients with high scores for all symptoms. Our study also demonstrated the complexity and diversity of symptom presentation in each patient, and we believe innovative methods such as clustering can capture and describe this more precisely.

Usually, HOA phenotyping is based on HOA localization or radiographic data. Kloppenburg et al. separated thumb based and interphalangeal HOA, which are clearly two different diseases in terms of risk factors, symptoms, and treatment (24). Marshall et al. identified four HOA clusters based on radiographic OA patterns and investigated their association with pain, function and grip strength (7). However, this was a radiographic-driven clustering approach far from the clinical perspective, whereas our research question was more clinically driven because we aimed to

identify clusters according to usual symptoms that can be easily assessed by using simple PROs such as the VAS or the AUSCAN self-administered questionnaire. Kazmers et al. identified family clustering of erosive HOA in state-wide population, but this analysis focused on risk factors (25). In other words, all these studies designed their clustering approach based on OA localization, radiographic OA or risk factors, but none explored the heterogeneity of symptoms, whereas the American College of Rheumatology and European League Against Rheumatism recommendations are driven by the symptoms and mention that the primary goal is to control symptoms such as pain and stiffness, optimize hand function and maximize activity participation and quality of life (26,27).

We then compared these clusters to help delineate some key features that differed among phenotypes. Bellamy et al. established a patient-acceptable symptomatic state (PASS) based on the AUSCAN score, with a threshold ≤ 41/100 (95% confidence interval [CI] 38-45) for pain, 38/100 (95% CI 33-44) for stiffness and 45 (95% CI 39-48) for physical function limitation (28). We found that only for patients in clusters 4 and 5 (N=122/389), corresponding to one-third of our cohort, were the mean AUSCAN sub-scores above the PASS thresholds for pain, stiffness, and physical function. Furthermore, those patients also presented a higher intake of weak opioids compared to other groups. These results agree with the need to better target patients with HOA in clinical care as well as in clinical trials (29).

According to Hodkinson et al., aesthetic discomfort on a VAS can be separated into low aesthetic concern ≤ 34 mm, intermediate concern 34–66 mm, and high aesthetic discomfort ≥ 66 mm (9). In our study, we observed an on/off distribution of aesthetic discomfort: clusters 1, 2 and 4

presented low aesthetic concerns, whereas both clusters 3 and 5 presented high aesthetic discomfort. We observed an on/off effect in our cohort because none of the clusters presented an intermediate concern. We confirmed an association between aesthetic discomfort nodes and erosive HOA as previously reported (9,30). In our study, sex, depression, and radiographic destruction were associated with increased symptom intensity but were not specific to aesthetic discomfort. We also found an association between symptoms and joint destruction but also between physical and psychological burden. Our findings may question the well-accepted notion of clinical and radiographic dissociation in OA.

Even though the number of patients with metabolic syndrome did not significantly differ among our clusters, 45·4 % of patients in the highly symptomatic cluster 5 presented a metabolic syndrome versus 26·1% in the cluster (p=0·013). Metabolic syndrome has been associated with HOA diagnosis in several studies, but a critical issue is whether the metabolic syndrome could amplify the intensity of symptoms (31,32). Sanchez-Santos et al. reported that metabolic syndrome was associated with more painful interphalangeal joints after adjustment on BMI and age, which suggests a specific role of metabolic syndrome in HOA (33). In our study, clusters with physical functional impairment presented significantly more thumb base pain. Fjellstad et al. described that reduced physical function was associated to ultra-sound detected synovitis inflammation in first carpo-metacarpal joints and not interphalangeal joints. Function was also the main patient expectation toward treatment, except in cluster 5, for which it was pain. These results demonstrate the importance of functional impairment as an HOA symptom and illustrate the recommendations of the ACR/Arthritis Foundation in which exercise, self-efficacy and self-management are strongly recommended for HOA (24).

Our study presented some limitations. The DIGICOD study is a hospital-based cohort in which HOA might be more severe, but patients were also recruited from private practice (18%). We assessed the stability, the significance, and the robustness of our clustering through several statistical methods; however, we did not externally validate our results in different HOA cohorts. This is a cross-sectional analysis and symptoms of HOA change throughout time. Indeed, cluster 1 could represent a less evolved group because patients were younger and had a lower average disease duration than other groups, especially cluster 5. The evolution of clusters and patient trajectories between clusters could be investigated in longitudinal analyses using the prospective 5-year follow-up of patients included in DIGICOD.

Our study raises many therapeutic perspectives. Our results support the need to quantitatively assess the patient with HOA by using simple PROs such as the VAS or AUSCAN. Such a precise assessment can lead to a tailored therapeutic management according to each cluster, with adapted exercise or self-management exercise and a focus on function but also a more pain-targeted strategy for one-third of our cohort. Additionally, this phenotypic delineation may help better target patient recruitment in clinical trials evaluating symptomatic drugs. Furthermore, our study highlights the importance of function in patients' main expectations.

In conclusion, we have identified five clinical clusters based on cardinal symptoms of HOA, which illustrates the wide variability and heterogeneity of the clinical presentation of HOA, emphasizes the need to clinically assess HOA patients quantitatively by using PROs for better management, and may lead to phenotype-based personalized medicine in HOA.

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Ethics

The DIGICOD study complies with the Declaration of Helsinki and obtained all the regulatory and ethics validation from local regulatory committee (Comité de Protection des Personnes, Paris Île-de-France IV).

Data availability

Anonymized data can be shared upon request. All requests should be made to JS. Data sharing will be subject to the terms of DIGICOD cohort and the AP-HP data-sharing agreement to ensure all users of the data adhere to the legal requirements of using personal data.

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Authors and contributions

All authors included met the four criteria for authorship in the ICJME recommendations (https://www.icmje.org). MB, EMF, JS conceived the study, AC, BC, MD, PR, FB, JS were responsible for data collection. JS, FB, AC, BC, MD, PR oversaw the clinical trials analysed in this study. MB, GP, NT analysed the data. MB, FC, AC, DK, AB, BC, MD, PR, EMF, FB, JS were involved in data interpretation. MB, EMF, JS wrote the first draft of the manuscript. All authors approved the final submitted version and agreed to publication. MB, GP, NT, EMF, JS had full access to all the data in the study. MB, EMF, FB, and JS had the final responsibility for the decision to submit for publication.

Competing interests

FC received consulting and lecture fees from UCB, Novartis and Lilly, AC received fees from Novartis, Pfizer and BMS. PR reports fees from Pfzier and Pierre Fabre. AB is a co-founder and consultant to Personalis and NuMedii; consultant to Samsung, Mango Tree Corporation, and in the recent past, 10x Genomics, Helix, Pathway Genomics, and Verinata (Illumina); has served on paid advisory panels or boards for Geisinger Health, Regenstrief Institute, Gerson Lehman Group, AlphaSights, Covance, Novartis, Genentech, and Merck, and Roche; is a shareholder in Personalis and NuMedii; is a minor shareholder in Apple, Facebook, Alphabet (Google), Microsoft, Amazon, Snap, 10x Genomics, Illumina, CVS, Nuna Health, Assay Depot, Vet24seven, Regeneron, Sanofi, Royalty Pharma, AstraZeneca, Moderna, Biogen, Paraxel, and Sutro, and several other non-health related companies and mutual funds; and has received honoraria and travel reimbursement for invited talks from Johnson and Johnson, Roche, Genentech, Pfizer, Merck, Lilly, Takeda, Varian, Mars, Siemens, Optum, Abbott, Celgene, AstraZeneca, AbbVie, Westat, and many academic institutions, medical or disease specific foundations and associations, and health systems. AB

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REFERENCES

1. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. The Lancet. 2019 Apr;393(10182):1745–59.

2. Qin J, Barbour KE, Murphy LB, Nelson AE, Schwartz TA, Helmick CG, et al. Lifetime Risk of Symptomatic Hand Osteoarthritis: The Johnston County Osteoarthritis Project. Arthritis Rheumatol. 2017 Jun;69(6):1204–12.

3. Altman R, Alarcon G, Appelrouth D, Bloch D, Borenstein D, Brandt K, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. Arthritis Rheum. 1990 Nov;33(11):1601–10.

4. Marshall M, Watt FE, Vincent TL, Dziedzic K. Hand osteoarthritis: clinical phenotypes, molecular mechanisms and disease management. Nat Rev Rheumatol. 2018 Nov;14(11):641–56.

5. Plotz B, Bomfim F, Sohail MA, Samuels J. Current Epidemiology and Risk Factors for the Development of Hand Osteoarthritis. Curr Rheumatol Rep. 2021 Aug;23(8):61.

6. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis Cartilage. 2007;15:A1–56.

7. Marshall M, van der Windt D, Nicholls E, Myers H, Dziedzic K. Radiographic thumb osteoarthritis: frequency, patterns and associations with pain and clinical assessment findings in a community-dwelling population. Rheumatology. 2011 Apr 1;50(4):735–9.

8. Favero M, Belluzzi E, Ortolan A, Lorenzin M, Oliviero F, Doria A, et al. Erosive hand osteoarthritis: latest findings and outlook. Nat Rev Rheumatol. 2022 Mar;18(3):171–83.

9. Hodkinson B, Maheu E, Michon M, Carrat F, Berenbaum F. Assessment and determinants of aesthetic discomfort in hand osteoarthritis. Ann Rheum Dis. 2012 Jan;71(1):45–9.

10. Kloppenburg M, Stamm T, Watt I, Kainberger F, Cawston TE, Birrell FN, et al. Research in hand osteoarthritis: time for reappraisal and demand for new strategies. An opinion paper. Ann Rheum Dis. 2007 Sep;66(9):1157–61.

11. Sellam J, Maheu E, Crema MD, Touati A, Courties A, Tuffet S, et al. The DIGICOD cohort: A hospital-based observational prospective cohort of patients with hand osteoarthritis – methodology and baseline characteristics of the population. Joint Bone Spine. 2021 Jul;88(4):105171.

12. Kellgren JH, Bier F. Radiological Signs of Rheumatoid Arthritis: A Study of Observer Differences in the Reading of Hand Films. Ann Rheum Dis. 1956 Mar 1;15(1):55–60.

13. Verbruggen G, Veys EM. Numerical scoring systems for the anatomic evolution of osteoarthritis of the finger joints. Arthritis Rheum. 1996 Feb;39(2):308–20.

14. Bellamy N, Campbell J, Haraoui B, Buchbinder R, Hobby K, Roth JH, et al. Dimensionality and clinical importance of pain and disability in hand osteoarthritis: Development of the Australian/Canadian (AUSCAN) Osteoarthritis Hand Index. Osteoarthritis Cartilage. 2002 Nov;10(11):855–62.

15. Neuprez A, Bruyère O, Dardenne N, Distèche S, Maheu E, Burlet N, et al. Assessment and determinants of aesthetic discomfort in hand osteoarthritis. Ann Rheum Dis. 2015 Oct;74(10):1942–1942.

16. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA J Am Med Assoc. 2001 May 16;285(19):2486–97.

17. Roberts HC, Denison HJ, Martin HJ, Patel HP, Syddall H, Cooper C, et al. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. Age Ageing. 2011 Jul;40(4):423–9.

18. Visser AW, Bøyesen P, Haugen IK, Schoones JW, van der Heijde DM, Rosendaal FR, et al. Radiographic scoring methods in hand osteoarthritis – a systematic literature search and descriptive review. Osteoarthritis Cartilage. 2014 Oct;22(10):1710–23.

19. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand. 1983 Jun;67(6):361–70.

20. Tibshirani R, Walther G, Hastie T. Estimating the number of clusters in a data set via the gap statistic. J R Stat Soc Ser B Stat Methodol. 2001;63(2):411–23.

21. Milligan GW, Cooper MC. An examination of procedures for determining the number of clusters in a data set. Psychometrika. 1985 Jun;50(2):159–79.

22. Hennig C. Cluster-wise assessment of cluster stability. Comput Stat Data Anal. 2007 Sep;52(1):258–71.

23. Kimes PK, Liu Y, Neil Hayes D, Marron JS. Statistical significance for hierarchical clustering: Statistical Significance for Hierarchical Clustering. Biometrics. 2017 Sep;73(3):811–21.

24. Kloppenburg M, van Beest S, Kroon FPB. Thumb base osteoarthritis: A hand osteoarthritis subset requiring a distinct approach. Best Pract Res Clin Rheumatol. 2017 Oct;31(5):649–60.

25. Kazmers NH, Meeks HD, Novak KA, Yu Z, Fulde GL, Thomas JL, et al. Familial Clustering of Erosive Hand Osteoarthritis in a Large Statewide Cohort. Arthritis Rheumatol. 2021 Mar;73(3):440–7.

26. Kloppenburg M, Kroon FP, Blanco FJ, Doherty M, Dziedzic KS, Greibrokk E, et al. 2018 update of the EULAR recommendations for the management of hand osteoarthritis. Ann Rheum Dis. 2019 Jan;78(1):16–24.

27. Bellamy N, Hochberg M, Tubach F, Martin-Mola E, Awada H, Bombardier C, et al. Development of Multinational Definitions of Minimal Clinically Important Improvement and Patient Acceptable Symptomatic State in Osteoarthritis: Multinational MCII and PASS Definitions for OA. Arthritis Care Res. 2015 Jul;67(7):972–80.

28. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Rheumatol. 2020 Feb;72(2):220–33.

29. Karsdal MA, Christiansen C, Ladel C, Henriksen K, Kraus VB, Bay-Jensen AC. Osteoarthritis – a case for personalized health care? Osteoarthritis Cartilage. 2014 Jan;22(1):7–16.

30. Neuprez A, Bruyère O, Maheu E, Dardenne N, Burlet N, D'Hooghe P, et al. Aesthetic discomfort in hand osteoarthritis: results from the LIège Hand Osteoarthritis Cohort (LIHOC). Arthritis Res Ther. 2015 Dec;17(1):346.

31. Mohajer B, Kwee RM, Guermazi A, Berenbaum F, Wan M, Zhen G, et al. Metabolic Syndrome and Osteoarthritis Distribution in the Hand Joints: A Propensity Score Matching Analysis From the Osteoarthritis Initiative. J Rheumatol. 2021 Oct;48(10):1608–15.

32. Tomi AL, Sellam J, Lacombe K, Fellahi S, Sebire M, Rey-Jouvin C, et al. Increased prevalence and severity of radiographic hand osteoarthritis in patients with HIV-1 infection associated with metabolic syndrome: data from the cross-sectional METAFIB-OA study. Ann Rheum Dis. 2016 Dec;75(12):2101–7.

33. Sanchez-Santos M, Judge A, Gulati M, Spector T, Hart D, Newton J, et al. Association of metabolic syndrome with knee and hand osteoarthritis: A community-based study of women. Semin Arthritis Rheum. 2019 Apr;48(5):791–8.

Table 1: AUSCAN sub-scores and VAS aesthetic score for clusters

	Overall (N=389)	Cluster 1 (N=88)	Cluster 2 (N=91)	Cluster 3 (N=80)	Cluster 4 (N=42)	Cluster 5 (N=88)
AUSCAN sub-scores (0-100), mean (SD)						
Pain	25·8 (21·4)	7·4 (5·8)	24·4 (12·9)	14·3 (12·6)	51·1 (20·5)	43·8 (20·0)
Stiffness	32·5 (28·1)	7·2 (6·0)	24·8 (16·6)	23·4 (17·3)	75·8 (17·2)	53·5 (25·7)
Physical function	36·1 (24·9)	11·1 (8·3)	38·9 (18·1)	22·9 (15·9)	57·3 (19·4)	60·1 (18·5)
VAS aesthetic (0-100 mm), mean (SD)	35·8 (34·4)	6·1 (9·2)	11·4 (13·1)	73·7 (20·2)	16·3 (16·3)	65·5 (24·6)

AUSCAN, Australian/Canadian osteoarthritis hand index; VAS, visual analogue scale; SD standard-deviation

Table 2: Descriptive analyses of the 19 descriptive clinical, biological, and radiological variables for clusters

	Overall (N=389)	Cluster 1 (N=88)	Cluster 2 (N=91)	Cluster 3 (N=80)	Cluster 4 (N=42)	Cluster 5 (N=88)	P value	Padj	Missing (%)
Demographic data									
Age (years), mean (SD)	66·5 (7·4)	64·9 (8·9)	65·7 (7·2)	65·9 (6·3)	68·3 (7·3) *	68·6 (6·4) **	0·004	0·032	0
Sex, n (%) Women	329 (84·6)	62 (70·5)	72 (79·1)	74 (92·5) ***	37 (88·1) *	84 (95·5) ***	<0·001	<0·001	0
Men	60 (15·4)	26 (29·5)	19 (20·9)	6 (7·5)	5 (11·9)	4 (4·5)			
Inflammatory and metabolism features									
BMI (kg/m^2), mean (SD)	25·1 (4·4)	24·8 (3·9)	26·0 (5·3)	24·4 (3·6)	26·0 (3·6)	24·7 (4·6)	0·072	ns	1·3
Metabolic syndrome (ATP III), n (%)	136 (35·0)	23 (26·1)	30 (33·0)	28 (35·0)	15 (35·7)	40 (45·5) *	0·24	ns	2·6
CRP ≥ 5 mg/L, n (%)	34 (8·7)	4 (4·5)	8 (8·8)	8 (10·0)	3 (7·1)	11 (12·5)	0·18	ns	17
HOA history									
HOA duration (years), mean (SD)	12·8 (9·7)	8·3 (6·6)	12·7 (9·7) **	13·6 (9·5) ***	14·0 (9·4) ***	16·3 (10·8) ***	<0·001	<0·001	3·1
HOA family history, n (%)	263 (67·6)	65 (73·9)	62 (68·1)	57 (71·2)	22 (52·4)	57 (64·8)	0·34	ns	3·1
Clinical examination									
Main expectation, n (%) Aesthetic	30 (7·7)	7 (8·0) *	0 (0·0) *	18 (22·5)	0 (0·0)	5 (5·7)	<0·001	0·001	0
Function	194 (49·9)	48 (54·5)	48 (52·7)	32 (40·0)	26 (61·9)	40 (45·5)			
Pain	164 (42·2)	32 (36·4)	43 (47·3)	30 (37·5)	16 (38·1)	43 (48·9)			
Grip strength dominant hand (kg), mean (SD)	26·1 (12·6)	31·8 (14·8)	28·3 (12·0) ***	24·0 (9·3) ***	21·9 (10·6) ***	21·8 (11·7) ***	<0·001	<0·001	0
Thumb base pain, n (%)	85 (21·9)	12 (13·6)	28 (30·8) *	9 (11·2)	10 (23·8)	26 (29·5) *	<0·001	0·0028	0
Number of swollen joints (0–30), mean (SD)	1·2 (2·1)	0·8 (1·8)	1·1 (2·3)	1·4 (2·7)	0·9 (1·7)	1·7 (1·8) ***	<0·001	0·002	0·3
Number of pressure pain joints (0–30), mean (SD)	4·6 (4·5)	2·6 (3·4)	4·0 (3·5) ***	3·9 (3·6) **	7·2 (6·0) ***	6·7 (4·9) ***	<0·001	<0·001	0

Number of nodes (0–30), mean (SD)	12·3 (7·5)	10·1 (6·8)	11·0 (8·0)	13·1 (6·8) **	12·7 (6·7)	14·8 (7·8) ***	<0·001	0·002	0
HADS score (0-21), mean (SD)	12·6 (6·0)	10·7 (5·3)	11·9 (5·6)	12·1 (5·7)	14·0 (6·5) **	15·0 (6·6) ***	<0·001	<0·001	0·8
Radiographic OA									
Erosive HOA (≥ 2 erosive joints), n (%)	134 (34·4)	19 (21·6)	30 (33·0)	31 (38·8)	11 (26·2)	43 (48·9)	0·002	0·014	0
KL sum score for both hands (0-128), mean (SD)	46·1 (17·7)	37·9 (17·5)	43·2 (18·2)	48·0 (17·2) **	48·9 (16·0) **	54·6 (14·3) ***	<0·001	<0·001	4·1
Analgesics									
NSAIDs, n (%)	83 (21·3)	9 (10·2)	22 (24·2) *	17 (21·2)	10 (23·8)	25 (28·4) **	0·047	ns	1·3
Paracetamol, n (%)	124 (31·9)	17 (19·3)	33 (36·3) *	21 (26·2)	15 (35·7)	38 (43·2) **	0.008	ns	1·3
Weak Opioids n (%)	34 (8·7)	3 (3·4)	6 (6·6)	6 (7·5)	6 (14·3) *	13 (14·8) *	0·049	ns	1.3

p_{adj}, p-adjusted; SMD, standard mean difference; SD: standard-deviation, OA: osteoarthritis; BMI, body mass index; ATP, adult treatment panel; CRP, C-reactive protein; HADS: Hospital Anxiety and Depression Scale; KL, Kellgren-Lawrence. ⁎ are corresponding of p-values of post hoc analysis of cluster 2-5 vs cluster 1 * p <0.05 ** p< 0.01 *** p<0.001

FIGURE LEGENDS

Figure 1: Flow chart of the DIGICOD cohort at baseline. AUSCAN: Australian/Canadian osteoarthritis hand index, VAS: visual analogue scale

Figure 2: Hierarchical agglomerative clustering of the 5 clinical clusters. Dendrogram and expression heatmap of each cluster based on AUSCAN physical function, stiffness, and pain sub-scores and VAS score for aesthetics. Each score is scaled between 0 and 1. For each individual, high scores are in red and low scores in blue. AUSCAN: Australian/Canadian osteoarthritis hand index, VAS: visual analogue scale

Figure 3: Radar plot and composition of the 5 clinical clusters. Each variable is represented by the mean of AUSCAN sub-scores for pain, physical function, and stiffness and the VAS aesthetic score on a circular scale. AUSCAN: Australian/Canadian osteoarthritis hand index, VAS: visual analogue scale

SUPPLEMENTARY FILES

Table S1: Post hoc analyses p-values in comparisons with reference cluster 1

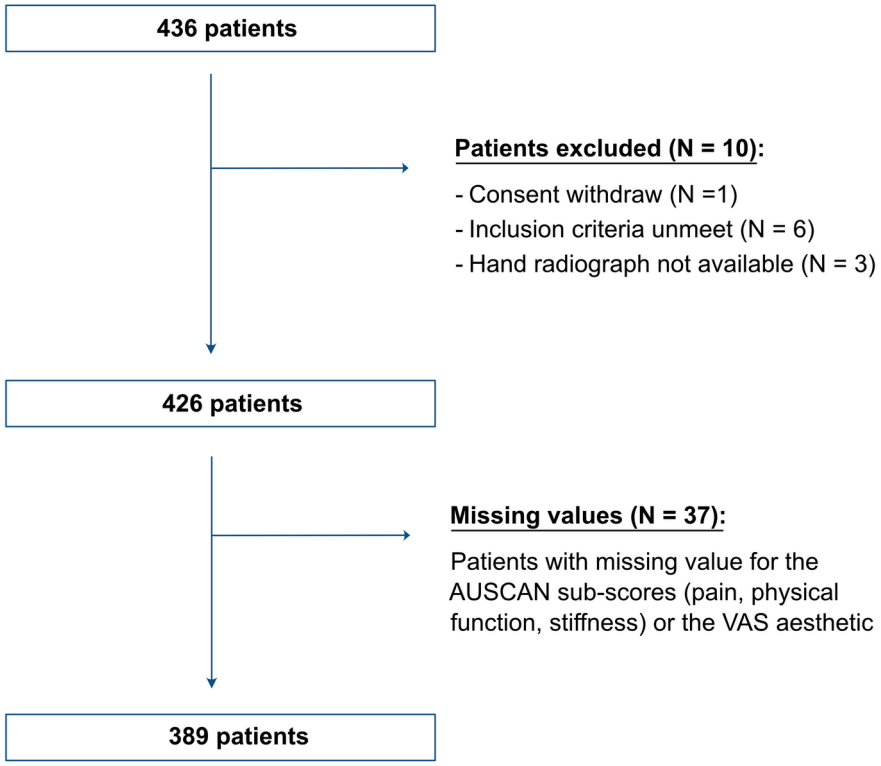
Figure S1: Multi-Dimensional Scaling projection of the clusters

Figure S3: Elbow plot for determining the optimal number of clusters based on the total within sum of square method

Figure S3: Gap statistic plot for determining the optimal number of clusters with the within cluster dispersion and a bootstrapping N = 200.

Figure S4: Histogram of Jaccard Similarity index among different clusters with a non-parametric bootstrapping (N = 200)

Figure S5 Boxplots and bar plots of the 19 descriptive variables. In boxplots, horizontal lines are median, box edges are interquartile range and whiskers are range; otherwise, data are percentages. BMI, body mass index; CRP, C-reactive protein; HADS, Hospital Anxiety and Depression Scale; KL, Kellgren-Lawrence, NSAID: Non-Steroidal Anti-Inflammatory Drugs



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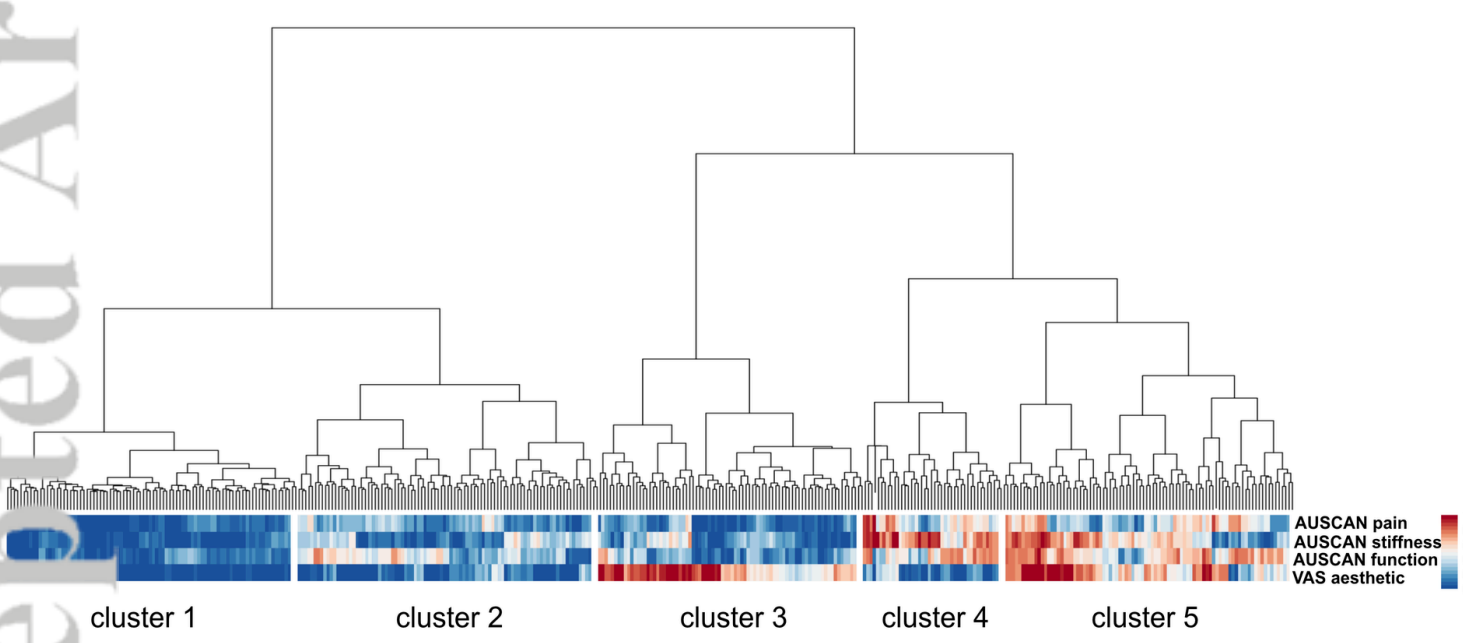

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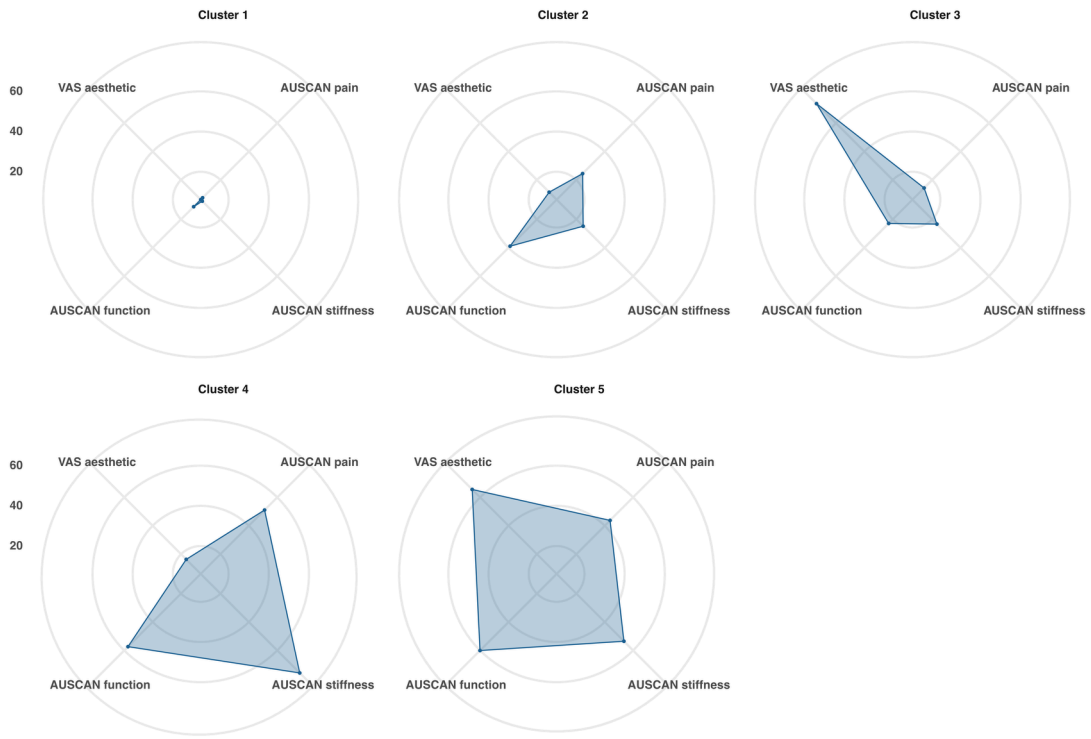

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