**Onset of comorbidities and flare patterns within pre-existing morbidity clusters in people with gout: 5-year primary care cohort study**

Authors

**Ram Bajpai**

Primary Care Centre Versus Arthritis, School of Medicine, Keele University, Staffordshire, ST5 5BG, UK. E-mail: [r.bajpai@keele.ac.uk](mailto:r.bajpai@keele.ac.uk)

**Sara Muller**

Primary Care Centre Versus Arthritis, School of Medicine, Keele University, Staffordshire, ST5 5BG, UK. E-mail: [s.muller@keele.ac.uk](mailto:s.muller@keele.ac.uk)

**Christian Mallen**

Primary Care Centre Versus Arthritis, School of Medicine, Keele University, Staffordshire, ST5 5BG, UK. E-mail: [c.d.mallen@keele.ac.uk](mailto:c.d.mallen@keele.ac.uk)

**Lorraine Watson**

Primary Care Centre Versus Arthritis, School of Medicine, Keele University, Staffordshire, ST5 5BG, UK. E-mail: [l.watson@keele.ac.uk](mailto:l.watson@keele.ac.uk)

**Pascal Richette**

APHP, Hôpital Lariboisière, Service de Rhumatologie, F-75010 Paris. France. E-mail: [pascal.richette@aphp.fr](mailto:pascal.richette@aphp.fr)

Université de Paris, Inserm, UMR-S 1132, Bioscar, F-75010 Paris, France

**Samantha L Hider**

Primary Care Centre Versus Arthritis, School of Medicine, Keele University, Staffordshire, ST5 5BG, UK.

Haywood Academic Rheumatology Centre, Midland Partnership NHS Foundation Trust, Haywood Hospital, High Lane, Burslem, Staffordshire, ST6 7AG, UK. E-mail: [s.hider@keele.ac.uk](mailto:s.hider@keele.ac.uk)

**Edward Roddy**

Primary Care Centre Versus Arthritis, School of Medicine, Keele University, Staffordshire, ST5 5BG, UK. E-mail: [e.roddy@keele.ac.uk](mailto:e.roddy@keele.ac.uk)

Haywood Academic Rheumatology Centre, Midland Partnership NHS Foundation Trust, Haywood Hospital, High Lane, Burslem, Staffordshire, ST6 7AG, UK.

**Correspondence to**:

**Ram Bajpai**

Primary Care Centre Versus Arthritis, School of Medicine, Keele University, Staffordshire, ST5 5BG, UK. E-mail: [r.bajpai@keele.ac.uk](mailto:r.bajpai@keele.ac.uk)

**Abstract**

**Objective**

To investigate the onset of comorbidities and pattern of flares over five years according to baseline comorbidity clusters in people with gout.

**Methods**

In a prospective primary-care-based cohort study, adults aged ≥18 years with gout, were identified from primary care medical records in 20 general practices across the West Midlands, UK and followed-up over five years. Four clusters of participants have been defined previously according to baseline comorbidity status. The associations of (i) incident comorbidities and (ii) gout flares with baseline cluster membership were estimated using age and sex-adjusted Poisson regression and mixed effects ordinal logistic regression, respectively.

**Results**

The comorbidity with the highest incidence was coronary artery disease (39.2%), followed by hypertension (36.7%), chronic kidney disease stage ≥3 (18.1%), obesity (16.0%), hyperlipidaemia (11.7%), diabetes (8.8%), and cancer (8.4%). There were statistically significant associations observed between cluster membership and incidence of coronary artery disease, hyperlipidaemia, heart failure, and hypertension. In each cluster, nearly one-third of participants reported ≥2 gout flares at each time-point. History of oligo/polyarticular flares (odds ratio [OR]: 2.16; 95% confidence interval [CI]: 1.73-2.70), and obesity (1.66; 1.21-2.25) were associated with increasing flares whereas current use of allopurinol was associated with lower risk (0.42; 0.34-0.53). Cluster membership was not associated with flares.

**Conclusion**

Substantial numbers of people in each cluster developed new comorbidities that varies by cluster membership. People also experienced multiple flares over time, but these did not differ between clusters. Clinicians should be vigilant for the development of new comorbidities in people with gout.

Keywords: Gout, Comorbidity clusters, Gout flares, Incidence, CVD risk factors, Prospective cohort study

**Rheumatology key messages**

* A substantial number of patients with gout developed new comorbidities over time.
* Incidence of coronary artery disease, hyperlipidaemia, heart failure, and hypertension differed according to baseline comorbidity cluster membership.
* Gout flare frequency was associated with obesity and previous oligo/polyarticular flares, but not baseline comorbidity cluster membership.

**Introduction**

Gout is the most common inflammatory arthritis and affects 2.5% of adults in the UK.[1] It is associated with many different comorbidities including traditional cardiovascular risk factors such as hypertension, obesity, hyperlipidaemia, coronary artery disease (CAD) and chronic kidney disease (CKD).[2] Comorbidities have a significant impact in people with gout, contributing to impaired quality of life and more frequent gout flares.[3-6]

Most existing studies of comorbidities in people with gout have focussed on the associations between gout and individual comorbidities, whereas comorbidities commonly co-exist. In the US Third National Health and Nutrition Survey, metabolic syndrome affected 63% of people with gout and was three times more likely in people with gout than age- and gender-matched controls without.[7] Cross-sectional studies from France and the UK have described discrete patterns of comorbidity clustering in people with gout.[8, 9] In people with gout recruited from primary care in the UK, there were four distinct comorbidity clusters.[8] These comprised a cluster with highly prevalent CKD, one with isolated gout and few comorbidities, a third cluster with multiple comorbidities, and a fourth with prevalent obesity and hypertension. Cluster membership was associated with flare frequency, tophi, gout treatments and healthcare utilisation.[8, 9] However, less is known about whether cluster membership is associated with development of new comorbidities or flare frequency longitudinally. A study from Taiwan undertook latent transition analysis to investigate longitudinal relationships between groups of comorbidities in men with incident gout, identifying three latent comorbidity classes.[10] Over time, most patients did not move class although small proportions moved to the class with a high prevalence of comorbidities particularly hypertension.

Therefore, the objectives of this study were to determine whether baseline comorbidity cluster membership was associated with 1) the onset of comorbidities and 2) more frequent flares over time.

**Methods**

Design and participants

The study used data from a primary-care-based prospective cohort study of adults aged 18 years and over with gout, registered with 20 general practices across the West Midlands, UK. Ethical approval was obtained from North West - Liverpool East Research Ethics Committee (REC reference number: 12/NW/0297). Full details of the cohort design are published elsewhere.[11] Participants with gout were identified through electronic primary care records of participating general practices using specific Read codes for gout, or a prescription for allopurinol or colchicine in the preceding two years.

Follow-up and questionnaire data

All participants who completed a baseline questionnaire and provided consent to future contact were mailed follow-up questionnaires at 12, 24, 36, 48 and 60 months. Questionnaire content included gout characteristics (flare frequency, history of oligo/polyarticular flares (flares affecting more than one joint simultaneously), age at diagnosis, allopurinol treatment), self-reported height and weight (used to calculate body mass index [BMI]), and socio-demographic characteristics (frequency of alcohol consumption, relationship status, attendance at further education). Participants were asked to report the number of self-reported gout attacks (flares) (0, 1, 2, 3, 4, ≥5) in the last 12 months at baseline and 24-, 36-, 48- and 60-month follow-up and in the last 6 months at 6- and 12-month follow-up. Non-responders were mailed reminders after two and four weeks. At baseline, responders were also asked to provide consent for the research team to access their primary care medical record for information about comorbidities and prescriptions.

Comorbidities

Primary care medical records of consenters were reviewed for the two years before baseline and up to five years afterwards. Diagnosed hypertension, diabetes mellitus, hyperlipidaemia, liver disorders, CAD, heart failure, cancer, and renal calculi were ascertained via Read codes (coding system used in UK primary care). Free text was also used to identify recorded presence of tophi. Obesity was defined as BMI ≥30 kg/m2. Estimated glomerular filtration rate (eGFR) was extracted from the medical record, Chronic kidney disease (CKD) stage ≥3 was defined as an eGFR <60ml/min. Metabolic syndrome was defined as obesity and at least two of hyperlipidaemia, currently taking lipid-lowering agents, diabetes mellitus or hypertension.[8] Baseline comorbidity clusters were defined by the presence of comorbidities in the medical record in the two-year period prior to baseline and labelled to describe the most common comorbidities in each cluster C1: chronic kidney disease; C2: isolated gout with few comorbidities; C3: multiple comorbidities; and C4: obesity and hypertension, as previously reported.[8] Onset of a new comorbidity (as defined above) over the five-year follow-up period was defined as a record of a comorbidity that was not recorded in the two years before baseline.

Statistical analysis

The incidence of each comorbidity in the five years post-baseline was summarised overall and within the previously identified clusters. Prevalent cases of each comorbidity at baseline were excluded from the denominator. Age- and sex-adjusted incidence rate ratios (IRRs) with 95% confidence intervals (CIs) were calculated using Poisson regression to quantify the incidence of each comorbidity separately in each cluster compared with cluster 2 (isolated gout).

To assess factors associated with the number of gout flares, we included all responders who returned their questionnaire at any follow-up time. Number of reported gout flares (i.e., 0, 1, and ≥2) was modelled over time, using mixed effects ordered logistic regression with time as a random effect. Mixed models are suitable for repeated measurements, and allowed the inclusion of all available data in the presence of dropouts.[12] Odds ratios (ORs) and 95%CIs were estimated for comorbidity clusters from the multivariable model adjusted for demographic (current age, sex, BMI category, relationship status, attended further education, and alcohol frequency) and gout-related (age at gout onset, history of oligo/polyarticular flares, and currently taking allopurinol) factors. The proportional odds assumption was checked for the final model. Mean and variance adaptive Gauss–Hermite quadrature integration method with seven integration points was used to obtain precise estimates. Clinically meaningful interactions were also checked and included in the model (if p<0.1). All analyses were conducted using the Stata version 15.1 (StataCorp, College Station, Texas, USA), and two-sided p-value<0.05 was considered for statistical significance.

**Results**

1,079 individuals completed the baseline questionnaire and gave consent for medical record review at the five-year follow-up. Of these, 916 participants responded at least once during follow-up and were included in the gout flare analysis. We observed slight variation in the baseline cluster membership and gender distribution between available and dropout participants in gout flare (supplementary Table S1) analyses.

The comorbidity with the highest incidence over the follow-up was CAD (39.2%), followed by hypertension (36.7%), CKD stage ≥3 (18.1%), obesity (16.0%), hyperlipidaemia (11.7%), diabetes (8.8%), and cancer (8.4%) (Figure 1). CAD had the highest incidence in each cluster (C1: 56.8%; C2: 25.6%; C3: 44.4%; C4: 65.1%). Other common incident comorbidities across the clusters were hypertension (C1: 57.3%; C2: 29.3%; C3: 45.3%; C4: not applicable), obesity (C1: 20.6%; C2: 14.2%; C3: 15.9%; C4: 17.5%), diabetes mellitus (C1: 12.1%; C2: 8.4%; C3: 6.9%; C4: 7.5%), and CKD stage ≥3 (C1: 0.0%; C2: 13.2%; C3: 25.6%; C4: 22.5%). There were statistically significant associations between cluster membership and incidence of CAD (Cluster 1 [IRR: 1.73, 95%CI: 1.22-2.45, p=0.002], Cluster 3 [IRR: 1.55, 95%CI: 1.03-2.21, p=0.033], Cluster 4 [IRR: 2.31, 95%CI: 1.65-3.24, p<0.01]), heart failure (Cluster 3 [IRR: 3.71, 95%CI: 1.27-10.87, p=0.017]), hyperlipidaemia (Cluster 3 [IRR: 1.85, 95%CI: 1.06-3.21, p=0.030], Cluster 4 [IRR: 1.99, 95%CI: 1.20-3.33, p=0.008]), and hypertension (Cluster 1 [IRR: 1.46, 95%CI: 1.00-2.12, p=0.048]) (Figure 1).

The number of gout flares in the past year stratified by cluster at each follow-up is presented in supplementary Table 2. At each follow-up time, the majority of participants experienced either no flare or one flare in all clusters. The prevalence of two or more gout flares was similar across clusters at baseline (range: 42.9% to 47.2%) however this reduced substantially over five-year follow-up in each cluster (range: 27.7% to 31.2%) (Supplementary table S2). Fully adjusted regression analysis presented in Table 1 showed no statistical difference in the odds of gout flares over time between clusters compared to cluster 2 (Cluster 1 [OR: 1.21, 95%CI: 0.72-2.02, p=0.461]; Cluster 3 [OR: 0.78, 95%CI: 0.50-1.22, p=0.269]; Cluster 4 [OR: 0.73, 95%CI: 0.42-1.27, p=0.267]). However, other baseline factors associated with gout flares were history of oligo/polyarticular flares (OR: 2.16, 95%CI: 1.73-2.70, p<0.001), and being obese (OR: 1.66, 95%CI: 1.21-2.25, p=0.001), current age (OR: 0.98, 95%CI: 0.97-0.99, p=0.007) and use of allopurinol (OR: 0.42, 95%CI: 0.34-0.53, p<0.001) appeared protective. Statistically significant interaction was also observed between cluster membership (especially cluster 2 and 3) and oligo/polyarticular gout, and cluster 3 and being overweight at baseline.

**Discussion**

In this five-year prospective cohort study, the most common incident comorbidity in people with prevalent gout was CAD followed by hypertension, obesity, CKD and diabetes. Incidence of CAD, heart failure, hyperlipidaemia and hypertension differed according to baseline comorbidity cluster membership. Most participants reported no or one gout flare in the previous year at each time-point and the occurrence of gout flares over five-years did not differ significantly between clusters. However, frequent gout flares were associated with a history of oligo- or polyarticular flares, obesity, and not taking allopurinol at baseline.

Few existing studies have examined how comorbidity clustering in patients with gout affects the onset of new comorbidities longitudinally. A latent transition analysis undertaken in the Taiwan Longitudinal Health Insurance Database identified three comorbidity classes in men with incident gout which the authors labelled hypertension with high prevalence of gout-related comorbidities (class 1), hypercholesterolemia with moderately prevalent comorbidities (class 2), and low prevalence of comorbidities (class 3).[10] Most patients did not move between classes over the ten-year follow-up period although a small number in classes 2 and 3 moved to class 1. The incidence rates of different comorbidities in patients with gout have been examined in studies from UK primary care. In the Clinical Practice Research Datalink, within 10 years after first diagnosis of gout 31% of patients developed hypertension and 20% diabetes. This incidence of diabetes is higher than the 5-year incidence in our study, whereas incidence of myocardial infarction (4%) and renal disease (8%) were lower.[2] To our knowledge, ours is the first study to date to compare longitudinal onset of individual comorbidities between comorbidity clusters. Previous studies have suggested that individual comorbidities such as cardiovascular disease, renal failure, hypertension and obesity are associated with recurrent gout flares.[4-6] Cross-sectional studies suggest that flares are more frequent in clusters in which CKD and heart disease are prevalent.[8, 9] However, we could not replicate these findings in our study.

Strengths of our study include the primary care setting which should ensure generalisability to most patients with gout and ascertainment of comorbidities using medical records. Another strength was the longitudinal design and length of follow-up to explore how incidence of comorbidities and gout flares were associated with the excess risk in each cluster. Limitations of our study include substantial loss to follow-up which is not surprising in a cohort study with multiple follow-up time-points. Background characteristics were mostly similar between responders and non-responders. We identified participants based on a gout consultation or prescription of allopurinol or colchicine in primary care, rather than crystal identification or validated criteria, risking misclassification. However, a GP diagnosis of gout has been shown previously to have a positive predictive value of at least 90%.[13, 14] Allopurinol and colchicine may occasionally be prescribed for indications other than gout, however, we have reported previously that participants identified by prescriptions without a gout consultation in the study period did not have Read codes for these alternative diagnoses.[15] Reliance on self-reported questionnaire data on gout flares may introduce recall bias, especially if other joint pains are interpreted as flares by participants. Since we commenced our study, a gout flare definition has been validated.[16] As this is a prevalent gout cohort different, results may be seen in an inception cohort recruited at gout diagnosis. A further limitation is that we did not assess adherence to allopurinol.

This prospective study investigated the influence of clustering on the incidence of comorbidities and gout flares. Future research could examine whether comorbidity cluster membership changes over time and longitudinal patterns of comorbidity clustering, and further explore the influence of clustering on flare frequency. The findings reinforce the need for screening people with gout for cardiovascular risk factors and renal function, guide clinicians as to which comorbidity phenotypes are at particular risk of developing new comorbidities, and support the provision of integrated care for comorbidities.

**Acknowledgements**

We would like to thank all participating practices, Keele CTU, and patients who participated in this study. C.M. is funded by the National Institute for Health Research (NIHR) Applied Research Collaboration West Midlands and the NIHR School for Primary Care Research. Views expressed are those of the authors and not necessarily those of the NHS, NIHR or the Department of Health and Social Care.

*Funding:* No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to conduct the work described in this manuscript.

*Disclosure statement:* The School of Medicine has received funding from Bristol Myers Squibb to support recruitment to an unrelated non-pharmacological Atrial Fibrillation study.

*Data Availability Statements:* Data are available upon reasonable request via open or restricted access through a strict controlled access procedure. In the first instance data requests and enquiries should be directed to medicine.datasharing@keele.ac.uk.

**Supplementary data**

Supplementary data are available at Rheumatology online.

**References**

1 Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. Annals of the rheumatic diseases 2015;74(4):661-7.

2 Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Comorbidities in patients with gout prior to and following diagnosis: case-control study. Annals of the rheumatic diseases 2016;75(1):210-7.

3 Chandratre P, Mallen C, Richardson J, et al. Health-related quality of life in gout in primary care: Baseline findings from a cohort study. Seminars in arthritis and rheumatism 2018;48(1):61-9.

4 Nguyen UD, Zhang Y, Louie-Gao Q, et al. Obesity Paradox in Recurrent Attacks of Gout in Observational Studies: Clarification and Remedy. Arthritis care & research 2017;69(4):561-6.

5 Pillinger MH, Bangalore S, Klein AB, Baumgartner S, Morlock R. Cardiovascular Disease and Gout: Real-World Experience Evaluating Patient Characteristics, Treatment Patterns, and Health Care Utilization. Journal of managed care & specialty pharmacy 2017;23(6):677-83.

6 Rothenbacher D, Primatesta P, Ferreira A, Cea-Soriano L, Rodriguez LA. Frequency and risk factors of gout flares in a large population-based cohort of incident gout. Rheumatology (Oxford, England) 2011;50(5):973-81.

7 Choi HK, Ford ES, Li C, Curhan G. Prevalence of the metabolic syndrome in patients with gout: the Third National Health and Nutrition Examination Survey. Arthritis and rheumatism 2007;57(1):109-15.

8 Bevis M, Blagojevic-Bucknall M, Mallen C, Hider S, Roddy E. Comorbidity clusters in people with gout: an observational cohort study with linked medical record review. Rheumatology (Oxford, England) 2018;57(8):1358-63.

9 Richette P, Clerson P, Perissin L, Flipo RM, Bardin T. Revisiting comorbidities in gout: a cluster analysis. Annals of the rheumatic diseases 2015;74(1):142-7.

10 Huang CF, Liu JC, Huang HC, Chuang SY, Chen CI, Lin KC. Longitudinal transition trajectory of gouty arthritis and its comorbidities: a population-based study. Rheumatology international 2017;37(2):313-22.

11 Chandratre P, Mallen C, Richardson J, et al. Prospective observational cohort study of Health Related Quality of Life (HRQOL), chronic foot problems and their determinants in gout: a research protocol. BMC musculoskeletal disorders 2012;13:219.

12 Rabe-Hesketh S, Skrondal A. *Multilevel and Longitudinal Modeling Using Stata*. 3 ed. Texas, USA: Stata Press; 2012.

13 Hassey A, Gerrett D, Wilson A. A survey of validity and utility of electronic patient records in a general practice. BMJ 2001;322(7299):1401-5.

14 Meier CR, Jick H. Omeprazole, other antiulcer drugs and newly diagnosed gout. Br J Clin Pharmacol 1997;44(2):175-8.

15 Watson L, Belcher J, Nicholls E, Muller S, Mallen C, Roddy E. Latent Class Growth Analysis of Gout Flare Trajectories: A Three-Year Prospective Cohort Study in Primary Care. Arthritis & Rheumatology 2020;72(11):1928-35.

16 Gaffo AL, Dalbeth N, Saag KG, et al. Brief Report: Validation of a Definition of Flare in Patients With Established Gout. Arthritis & Rheumatology 2018;70(3):462-7.

Figure 1. Incidence of comorbidities stratified by comorbidity clusters and age and sex adjusted

incidence rate ratios (IRRs) with 95% confidence intervals



Table 1: Multilevel mixed effect ordered logistic regression analysis to explore factors associated with number of gout flares annually over five years

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Baseline characteristics** | **Unadjusted** | | | **Adjusted** | | |
| **OR** | **95% CI** | **P value** | **OR** | **95% CI** | **P value** |
| Clusters |  |  |  |  |  |  |
| 1 (chronic kidney disease) | 0.92 | 0.77-1.09 | 0.331 | 1.21 | 0.72-2.02 | 0.467 |
| 2 (isolated gout) | 1 (Ref.) |  |  | 1 (Ref.) |  |  |
| 3 (multiple comorbidities) | 0.88 | 0.76-1.02 | 0.099 | 0.78 | 0.50-1.22 | 0.269 |
| 4 (obesity and hypertension) | 0.91 | 0.77-1.08 | 0.282 | 0.73 | 0.42-1.27 | 0.261 |
| History of oligo/polyarticular flares |  |  |  |  |  |  |
| No | 1 (Ref.) |  |  | 1 (Ref.) |  |  |
| Yes | 2.58 | 2.27-2.93 | p<0.001 | 2.16 | 1.73-2.70 | p<0.001 |
| Currently take allopurinol |  |  |  |  |  |  |
| No | 1 (Ref.) |  |  | 1 (Ref.) |  |  |
| Yes | 0.47 | 0.41-0.54 | p<0.001 | 0.42 | 0.34-0.53 | p<0.001 |
| Age at questionnaire completion (years) | 0.99 | 0.98-0.99 | p<0.001 | 0.98 | 0.97-0.99 | 0.007 |
| Age at gout diagnosis (years) | 0.99 | 0.99-1.00 | 0.456 | 1.00 | 0.99 - 1.00 | 0.444 |
| Gender |  |  |  |  |  |  |
| Female | 1 (Ref.) |  |  | 1 (Ref.) |  |  |
| Male | 0.97 | 0.81-1.16 | 0.730 | 1.14 | 0.90-1.45 | 0.289 |
| BMI category |  |  |  |  |  |  |
| Normal | 1 (Ref.) |  |  | 1 (Ref.) |  |  |
| Overweight | 1.25 | 1.05-1.48 | 0.010 | 1.04 | 0.78-1.38 | 0.800 |
| Obese | 1.66 | 1.40-1.98 | p<0.001 | 1.66 | 1.21-2.25 | 0.001 |
| Relationship status |  |  |  |  |  |  |
| Married/ cohabiting | 1 (Ref.) |  |  | 1 (Ref.) |  |  |
| Single | 1.06 | 0.92-1.23 | 0.432 | 1.01 | 0.85-1.20 | 0.947 |
| Attended further education |  |  |  |  |  |  |
| No | 1.15 | 0.99-1.32 | 0.059 | 1.01 | 0.86-1.19 | 0.892 |
| Yes | 1 (Ref.) |  |  | 1 (Ref.) |  |  |
| Alcohol frequency |  |  |  |  |  |  |
| Daily/3-4 times a week | 0.70 | 0.55-0.88 | 0.002 | 0.99 | 0.75-1.31 | 0.969 |
| 1-2 week/1-3 month | 0.87 | 0.68-1.10 | 0.239 | 1.15 | 0.87-1.53 | 0.326 |
| Special occasions | 1.00 | 0.76-1.33 | 0.975 | 1.21 | 0.88-1.67 | 0.243 |
| Never | 1 (Ref.) |  |  | 1 (Ref.) |  |  |
| ***Interaction terms (if P<0.1)*** |  |  |  |  |  |  |
| Clusters x history of oligo/polyarticular flares |  |  |  |  |  |  |
| 2 x No |  |  |  | 1 (Ref.) |  |  |
| 3 x Yes |  |  |  | 1.67 | 1.17-2.38 | 0.005 |
| 4 x Yes |  |  |  | 1.78 | 1.18-2.68 | 0.006 |
| Clusters x BMI category |  |  |  |  |  |  |
| 2 x Normal |  |  |  | 1 (Ref.) |  |  |
| 3 x Overweight |  |  |  | 2.02 | 1.28-3.21 | 0.003 |

BMI: body mass index; BMI categories: Normal (18.5-24.9 kg/m2), Overweight (25-29.9 kg/m2), and Obese (≥30 kg/m2); OR: odds ratio; CI: confidence interval; Ref.: reference category

**Supplementary Materials**

Table S1: Comparison of baseline characteristics between available and dropout patients in the gout flare analysis

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Baseline characteristics** | **Total (N=1079)** | **Available (N=916)** | **Dropouts (N=163)** | **P value** |
| Age, (mean, sd) | 65.5 (12.5) | 64.9 (12.2) | 68.7 (13.2) | p<0.001 |
| Age at gout diagnosis, (mean, sd) | 53.3 (15.8) | 53.1 (15.5) | 55.4 (18.5) | 0.176 |
| BMI!, (mean, sd) | 29.2 (5.1) | 29.2 (5.1) | 29.0 (5.1) | 0.178 |
| Gender, (n, %) |  |  |  | 0.016 |
| Male | 909 (84.2) | 782 (85.4) | 127 (77.9) |  |
| Female | 170 (15.8) | 134 (14.6) | 36 (22.1) |  |
| History of oligo/polyarticular flares!, (n, %) |  |  |  | 0.008 |
| Yes | 399 (38.7) | 341 (37.2) | 58 (50.0) |  |
| No | 633 (61.3) | 575 (62.8) | 59 (50.0) |  |
| Clusters, (n, %) |  |  |  | p<0.001 |
| 1 (chronic kidney disease) | 197 (18.3) | 148 (16.2) | 49 (30.1) |  |
| 2 (isolated gout) | 393 (36.4) | 348 (38.0) | 45 (27.6) |  |
| 3 (multiple comorbidities) | 296 (27.4) | 247 (27.0) | 49 (30.1) |  |
| 4 (obesity and hypertension) | 193 (17.9) | 173 (18.8) | 20 (12.3) |  |
| Currently take allopurinol!, (n, %) |  |  |  | 0.471 |
| No | 435 (42.7) | 528 (57.6) | 55 (53.9) |  |
| Yes | 583 (57.3) | 388 (42.4) | 47 (46.1) |  |
| BMI category!, (n, %) |  |  |  | 0.941 |
| Normal | 203 (19.7) | 179 (19.5) | 24 (20.5) |  |
| Overweight | 468 (45.3) | 414 (45.2) | 54 (46.2) |  |
| Obese | 362 (35.0) | 323 (35.3) | 39 (33.3) |  |
| Relationship status!, (n, %) |  |  |  | 0.015 |
| Married/ cohabiting | 810 (76.1) | 709 (77.4) | 101 (68.2) |  |
| Single | 254 (23.9) | 207 (22.6) | 47 (31.8) |  |
| Attended further education!, (n, %) |  |  |  | 0.246 |
| No | 796 (77.3) | 213 (23.3) | 21 (18.4) |  |
| Yes | 234 (22.7) | 703 (76.8) | 93 (81.6) |  |
| Alcohol frequency!, (n, %) |  |  |  | 0.039 |
| Daily/3-4 times a week | 491 (46.0) | 433 (47.3) | 58 (38.4) |  |
| 1-2 week/1-3 month | 334 (31.3) | 288 (31.4) | 46 (30.5) |  |
| Special occasions | 144 (13.5) | 114 (12.5) | 30 (19.9) |  |
| Never | 98 (9.2) | 81 (8.8) | 17 (11.2) |  |

!There were some missing cases at the baseline

Table S2: Number of gout flares by comorbidity cluster over the preceding 12 months at follow-up time-point

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **n** | **Number of gout flares (%)** | | |
| **0** | **1** | **≥2** |
| **Baseline (N=1,027)** |  |  |  |  |
| Cluster 1 | 180 | 29.4 | 23.3 | 47.2 |
| Cluster 2 | 379 | 34.6 | 21.6 | 43.8 |
| Cluster 3 | 280 | 38.2 | 18.9 | 42.9 |
| Cluster 4 | 188 | 37.2 | 17.6 | 45.2 |
| **12 months (N=683)** |  |  |  |  |
| Cluster 1 | 113 | 59.3 | 15.3 | 24.8 |
| Cluster 2 | 250 | 55.2 | 21.6 | 23.2 |
| Cluster 3 | 202 | 58.4 | 14.4 | 27.2 |
| Cluster 4 | 118 | 62.7 | 14.4 | 22.9 |
| **24 months (N=651)** |  |  |  |  |
| Cluster 1 | 107 | 54.2 | 14.0 | 31.8 |
| Cluster 2 | 245 | 49.0 | 18.4 | 32.7 |
| Cluster 3 | 177 | 53.7 | 14.1 | 32.2 |
| Cluster 4 | 122 | 50.8 | 16.4 | 32.8 |
| **36 months (N=563)** |  |  |  |  |
| Cluster 1 | 90 | 58.9 | 12.2 | 28.9 |
| Cluster 2 | 213 | 52.6 | 14.1 | 33.3 |
| Cluster 3 | 154 | 55.2 | 14.3 | 30.5 |
| Cluster 4 | 106 | 56.6 | 10.4 | 33.0 |
| **48 months (N=526)** |  |  |  |  |
| Cluster 1 | 81 | 63.0 | 12.4 | 24.7 |
| Cluster 2 | 208 | 51.0 | 14.9 | 34.1 |
| Cluster 3 | 134 | 59.7 | 11.2 | 21.1 |
| Cluster 4 | 103 | 59.2 | 10.7 | 30.1 |
| **60 months (N=387)** |  |  |  |  |
| Cluster 1 | 60 | 58.3 | 11.7 | 30.0 |
| Cluster 2 | 157 | 57.3 | 11.5 | 31.2 |
| Cluster 3 | 101 | 62.4 | 9.9 | 27.7 |
| Cluster 4 | 69 | 55.1 | 11.1 | 30.5 |

N: total number of non-missing gout flares data.