Title: Comorbidity clusters in people with gout: an observational cohort study with linked medical record review

Authors:

Megan Bevis[1]

Milisa Blagojevic-Bucknall[1]

Christian Mallen[1]

Samantha Hider[1,2]

Edward Roddy[1,2]

Affiliations:

[1] Arthritis Research UK Primary Care Centre, Research Institute for Primary Care & Health Sciences, Keele University, UK

[2] Haywood Academic Rheumatology Centre, Haywood Hospital, Staffordshire and Stoke-on-Trent Rheumatology Partnership NHS Trust, Stoke-on-Trent, UK

Corresponding author: Dr Edward Roddy; Arthritis Research UK Primary Care Centre, Research Institute for Primary Care & Health Sciences, Keele University, Keele, Staffordshire, ST5 3BG, United Kingdom; Tel: 00 44 1782 734715 ; Fax: 00 44 1782 734719; Email: e.roddy@keele.ac.uk

Running header: Comorbidity clusters in people with gout

ABSTRACT

Objective: To investigate how comorbid conditions cluster in patients with gout in a UK primary care population.

Methods: A cross-sectional study was performed using baseline data from a primary care-based prospective observational cohort of people aged ≥ 18 years with gout. Participants with gout were identified through primary care medical records. Factor analysis was performed to obtain distinct clusters of comorbidity variables including obesity, hypertension, diabetes mellitus, hyperlipidaemia, coronary heart disease, heart failure, chronic kidney disease and cancer. Hierarchical cluster analysis of patient observations was also performed to identify homogenous subgroups of patients based on combinations of their comorbidities.

Results: Four distinct comorbidity clusters (C1-C4) were identified in 1079 participants (mean age 65.5 years (SD 12.5); 909 (84%) male). Cluster C1 (n=197, 18%) was the oldest group and had the most frequent attacks of gout. 97% had chronic kidney disease. Participants in C2 (n=393, 36%) had isolated gout with few comorbidities but drank alcohol more frequently. In cluster C3 (n=296, 27%), hypertension, diabetes mellitus, hyperlipidaemia, coronary heart disease and/or chronic kidney disease were prevalent, and urate-lowering therapy was prescribed more frequently than in other clusters. All patients in C4 (193, 18%) had hypertension and were more likely to be obese than other clusters.

Conclusions: Four distinct comorbidity clusters were identified. People with multiple comorbidities were more likely to receive allopurinol. Tailoring of treatments depending on cluster and comorbidities should be considered.

Keywords: gout; comorbidities; primary care; alcohol; obesity

Key messages (up to 3, max 15 words each)

- Four distinct comorbidity clusters in gout with differing clinical phenotypes were identified.
- People with gout and frequent comorbidities were most likely to receive urate-lowering therapy.
- ~~Prescription of n~~Non-steroidal anti-inflammatory drugs ~~was~~were commonly prescribed, even amongst those with gout and chronic kidney disease.

Introduction

Gout is the most prevalent inflammatory arthritis, affecting 2.5% of adults in the UK [1]. It has complex associations with comorbidity with some medical conditions predisposing to gout whereas gout is itself a risk factor for other comorbidities. For example, obesity, hypertension, and obstructive sleep apnoea all predispose to the development of gout [2-4], whereas gout is an independent risk factor for incident cardiovascular disease, nephrolithiasis and erectile dysfunction [4-7]. Chronic kidney disease (CKD) is a risk factor for gout which can then in turn lead to deterioration of renal function and worsening CKD [4,8,9]. Common treatments for hypertension, cardiac and renal disease, particularly diuretics, are also risk factors for incident hyperuricaemia and gout [10]. Furthermore, the management of gout is often more complex in the presence of comorbidity, presenting a significant therapeutic challenge.

Most existing studies have considered the epidemiological relationships between gout and single comorbid conditions. Few have taken into account the frequent co-occurrence of multiple comorbidities although metabolic syndrome is three times more common in people with gout than age- and gender-matched controls without gout [11]. A recent French study was the first to examine how different comorbidities cluster together in people with gout, identifying five distinct comorbidity clusters ranging from a cluster characterised by people with isolated gout and few comorbidities to one with a very high prevalence of cardiac and renal disease [12].

The aims of this observational study therefore were to explore whether such comorbidity clusters are generalizable to people with gout in other settings, by examining the existence of comorbidity clusters among people with gout recruited from primary care in the UK, and to compare gout characteristics, comorbidities and prescribed medication between any clusters identified.

Methods

The study used baseline 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 [13]. Ethical approval was obtained from North West – Liverpool East Research Ethics Committee (REC reference number: 12/NW/0297). Full details of the study may be found elsewhere [13]. In summary, participants with gout were identified through electronic primary care records of participating general practices using specific Read codes for gout, or a prescription of allopurinol or colchicine in the preceding two years. Eligible patients were mailed a self-report questionnaire that requested information about different aspects of gout and their general health. Specific questions about gout included age at diagnosis, number of attacks experienced in the preceding 12 months, and history of gout attacks affecting more than one joint (oligo/polyarticular gout attacks). The questionnaire also asked about alcohol consumption and self-reported height and weight, from which BMI was calculated. Obesity was defined as BMI≥30 kg/m^2. Participants were asked to provide consent for the research team to review their medical records. Baseline responders who consented to medical record review formed the analysis sample for this study.

Medical records were reviewed for the preceding two years for primary care consultations, medications and comorbidities. Hypertension, diabetes mellitus, hyperlipidaemia, liver disorders, coronary heart disease (CHD), heart failure, cancer and the presence of renal calculi and tophi were ascertained via Read codes. Estimated glomerular filtration rate (eGFR) was also extracted from the medical record with CKD stage≥3 defined as eGFR<60ml/min and sub-divided into stage 3 (eGFR 30-59ml/min) and stage 4/5 (eGFR<30ml/min). The metabolic syndrome was defined as the presence of BMI>30kg/m^2 and at least two of the following: hyperlipidaemia, currently taking lipid-lowering agents,

diabetes mellitus, or hypertension [14]. The total number of primary care consultations during the two years prior to study entry was calculated.

Using relevant British National Formulary codes, prescriptions for non-steroidal anti-inflammatory drugs (NSAIDs), prednisolone, colchicine, allopurinol, aspirin, lipid-lowering drugs (other than fenofibrate), fenofibrate, diuretics, losartan and anti-hypertensive medications, were identified in the medical records of consenting participants during the preceding two years. Only five participants received non-allopurinol urate-lowering therapy hence only use of allopurinol was considered.

Lists of all Read codes used may be found in the morbidity section of the medical record data research repository at www.keele.ac.uk/mrr.

Statistical analysis

Age and BMI were summarised via mean and standard deviation, and gout duration and total number of primary care consultations by median and interquartile range (IQR), and categorical variables via frequencies and percentages. Clustering of comorbidities was first examined, aiming to establish any underlying factor structure among the comorbid conditions. For this purpose, principal components analysis was performed to extract factors using oblique rotation (direct oblimin, which assumes correlated factors), with eigenvalue > 1 criterion. A particular comorbidity loaded a factor if the value of the loading was highest for that factor. Comorbidities considered were: obesity, hypertension, diabetes mellitus, hyperlipidaemia, CHD, heart failure, CKD and cancer. Only two patients had a record of liver disorders hence this comorbidity was not considered in cluster analyses. Patients for whom BMI was missing were excluded from the main analysis, however subsequently, sensitivity of the findings to include missing BMI as a separate category was assessed. Comorbidities' correlation matrix was initially visually inspected for extreme multicollinearity. Subsequently

the Kaiser-Meyer-Olkin (KMO) test was performed to assess more formally the adequacy of data for factor analysis, taking test values of greater than 0.5 as acceptable; furthermore significance of Bartlett's measure, testing the null hypothesis that the correlation matrix is an identity matrix, was required [15]. As a sensitivity analysis, orthogonal rotation Varimax, which does not assume correlated factors, was used too. Next, agglomerative hierarchical cluster analysis, using Ward's minimum variance method [16] was performed to place patients into homogeneous groups based on combinations of their comorbidities, considering the same set as in the factor analysis. The algorithm started with each patient in their own cluster; at each subsequent step, clusters were combined in a way that minimized within cluster sum of squares and the process was repeated until one single cluster was obtained.

For diagnoses of comorbidities and indication of use of different drugs, it was assumed that those without a record of the relevant Read code or BNF code did not have the corresponding comorbidity or drug prescribed respectively.

Analyses were performed in SPSS for Windows.[17]

RESULTS

Survey response figures have been reported in detail elsewhere [18]. In summary, the baseline survey population consisted of 1805 patients, of whom nine were excluded during the mailing process due to death or serious health reasons. Of the remaining 1796 patients, 1184 (66%) responded to the baseline survey. Responders tended to be older, more likely to be male and live in less deprived areas compared than non-responders [18]. 1079 (91%) of responders consented to review of their medical records and formed the analysis sample. Characteristics of the sample and distribution of comorbidities and medication use are presented in tables 1 and 2.

Participants were predominantly male (84%) and mean age was 65.5 ± 12.5 years. Mean age at gout diagnosis was 53.3 ± 15.8 years. 666 (65%) participants reported having at least one gout attack in the last 12 months and 399 (39%) had a history of oligo/polyarticular attacks. The median number of primary care consultations in the preceding six months was 14 (interquartile range 4-28). Daily consumption of alcoholic drinks was reported by 259 (24%). Comorbidities were common, particularly obesity, hypertension and CKD. During the preceding two years, prescriptions for NSAIDs, allopurinol, and non-losartan anti-hypertensive medications were received by 60% of participants, while 58% received a prescription for lipid-lowering drugs and 27% for diuretics. Colchicine was prescribed for 32%.

Clustering of comorbidities

There were no extreme correlations >0.9 and no comorbidity that was completely uncorrelated with the other comorbidities. The KMO statistic was 0.587 and Bartlett's test was significant ($p<0.001$), implying that factor analysis was appropriate. Three factors were extracted accounting for 54.7% of the variance (table 3). These were: F1 diabetes, hyperlipidaemia and coronary heart disease, F2 obesity and heart failure, F3 hypertension and CKD. Addition of cancer reduced the total variance explained to 48.6% hence cancer was not included. Identical results were obtained when using orthogonal rather than oblique factor rotation (data not shown).

Clustering of patients

The same set of variables was used as in the factor analysis. Four comorbidity clusters (C1-C4) were identified and their characteristics are presented in tables 1 and 2.

Cluster C1 (n=197, 18%) had the lowest proportion of males (69%) and highest mean age and mean age at gout diagnosis (73 years, 63 years respectively) compared to other clusters. CKD was very common (97%; stage 3 79%; stage 4/5 18%) and almost half had hypertension; other comorbidities were infrequent. Furthermore, patients in C1 reported more gout attacks in the last 12 months and were more likely to be prescribed prednisolone, colchicine and diuretics compared to patients in other clusters. Almost half (49%), were prescribed NSAIDs. Participants in C2 (n=393, 36%) had the lowest mean age, lowest mean age at gout diagnosis, lowest mean BMI, very infrequent comorbidities, and lowest median number of consultations within two years prior to study entry compared to other clusters, but drank alcoholic drinks more frequently and were more likely to be prescribed NSAIDs. Most comorbidities were prevalent in C3 (296, 27%): coronary heart disease (52%), diabetes mellitus (50%), hypertension (49%), CKD (43%; stage 3 36%; stage 4/5 6%), hyperlipidaemia (36%) and metabolic syndrome (31%) were common. Over 80% received lipid-lowering drugs and antihypertensive medications, one-half were prescribed aspirin, and one-third diuretics. Participants in C3 had the longest duration of gout (median 11, IQR 4-22), had the highest median number of primary care consultations (23, IQR 14-39) and were more likely to be prescribed allopurinol compared to patients in other clusters. All patients in C4 (193, 18%) had hypertension and 44% were classed as obese, a higher proportion than in other clusters. Antihypertensive medications were prescribed for 85%.

DISCUSSION

This is one of the first studies to examine clustering of comorbidities in patients with gout. In our sample of patients with gout recruited from UK primary care, we identified four distinct comorbidity clusters (C1-C4). C1 comprised the oldest participants who reported the most frequent gout attacks. Despite almost all participants having CKD and prescription of

NSAIDs being less common in this cluster than others, almost one-half of participants were still prescribed an NSAID. C2 consisted of younger participants who had isolated gout with few comorbidities. In C3, hypertension, hyperlipidaemia, diabetes mellitus, CKD and/or coronary heart disease were prevalent. These participants had the longest duration of gout and were the most likely to receive ULT. All participants in C4 had hypertension and almost a half were obese. In clusters 1 and 3, most participants with CKD had stage 3 disease.

There has only been one previous study looking at clustering of comorbidities in gout, in which five clusters were identified (c1 isolated gout with few comorbidities; c2 obesity with hypertension; c3 mostly diabetic; c4 predominant dyslipidaemia; and c5 cardiovascular disease and renal failure) [12]. Although our analysis found one cluster fewer than this study, there are some similarities between the findings. Both studies identified an isolated cluster with few comorbidities and a more severe cluster with highly prevalent CKD. The isolated gout cluster had few recognised risk factors for gout, other than a third being obese and a third consuming at least moderate volumes of beer per week, raising the possibility that genetic factors could be of particular relevance in this cluster. Unfortunately, we did not ask about family history of gout so could not explore this further. Although both studies ascertained a cluster with prevalent obesity and hypertension, in the study by Richette et al [12] other comorbidities were common in this cluster in contrast to our study. Their remaining clusters comprised different combinations of multiple traditional cardiovascular risk factors whereas we could only identify a single additional cluster. These differences may reflect our smaller sample size or that our participants were recruited exclusively from primary care. Richette et al recruited from both primary and secondary care and hence may have recruited a more severely affected cohort, as suggested by the considerably higher prevalences of tophi, renal calculi and all comorbidities (except for CHD and renal failure) than seen in our sample. In our study, the isolated gout cluster with few comorbidities was the

largest (36%) in contrast to Richette et al where it comprised only 12% of the study sample. A further discrepancy between our study and that of Richette et al is that liver disorders were very infrequent in our population. This could reflect either differing methods of ascertainment or differences in the severity of the two cohorts. Our study also makes important observations about the treatment of gout. Participants with frequent comorbidities (C3) were more likely to receive ULT than those in other clusters, as has been shown in several other studies [19-21]. In contrast, people with CKD (C1) had the most frequent attacks of gout yet the lowest rates of ULT prescription, highlighting the challenges of treating gout in CKD. It is also noteworthy that 49% of participants in C1 were prescribed NSAIDs despite CKD being a contra-indication to NSAID use, risking further deterioration in renal function.

Previous research has suggested that lipid levels play a central role in determining serum urate levels. In a study of obese patients undergoing bariatric surgery, pre-operative serum urate levels correlated with triglyceride levels and BMI, and post-operatively the decrease in serum urate correlated with reductions in triglyceride levels and BMI but not xanthine oxidase activity or insulin resistance [22]. The authors postulated that reductions in serum urate levels associated with weight loss might be partly attributable to increased renal urate excretion secondary to lowering of triglyceride levels. It is interesting therefore that in our study the proportion with obesity was similar between the four clusters (range 29-44%) but hyperlipidaemia was seen only in C3 where other comorbidities were also commonplace. Low high-density lipoprotein and high total cholesterol levels are also associated with failure to reach a target serum urate level in patients receiving ULT [23]. Unfortunately, serum urate levels are often infrequently measured in clinical practice in primary care and hence we were unable to make meaningful comparisons of serum urate levels between the clusters as serum urate levels had been checked in only a minority of participants (n=461). CKD and diuretic

use are also important risk factors for hyperuricaemia and gout. In both clusters with prevalent CKD (C1 and C3), use of diuretics was frequent as well as other medications which may predispose to hyperuricaemia and gout particularly beta-blockers and angiotensin-converting enzyme inhibitors [24]. Hence, multiple factors may be contributing to hyperuricaemia in these clusters.

The strengths of this study include the statistical methodology and the primary care setting ensuring relevance of our findings to the majority of people with gout who are managed exclusively in primary care. The diagnosis of gout was based on diagnosis by a GP, risking misclassification bias, however our previous studies have shown that this does not seem to occur frequently [252,263]. Misclassification of comorbidities is also possible, however, this is less likely to be significant as comorbidities were ascertained from participants' medical records rather than relying on participant self-report.

Our findings support the generalisability of the comorbidity clusters in gout previously reported by Richette et al [12]. Further research is needed to explore pathophysiological processes in these clusters such as the roles of genetic factors and dyslipidaemia, and the relative contributions of renal disease and medications~~how these clusters relate to pathophysiological processes~~. Prospective studies should investigate the influence of clustering of comorbidities on the prognosis and natural history of gout and the risk of developing incident gout, as well as how clustering changes with time and whether participants move between clusters. Whilst people with multiple comorbidities seem more likely to receive ULT, better efforts are required to offer treatment to those with isolated gout and to optimise treatment in people with CKD who appear to have more severe gout in this study.

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Declaration of interests

The authors have no conflicts of interest to declare.

References:

1. Kuo CF, Grainge MJ, Mallen CD, Zhang W, Doherty M. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. Ann Rheum Dis 2014;74:661-7.

2. Roddy E, Choi HK. Epidemiology of gout. Rheum Dis Clin North Am 2014;40:155–75.

3. Zhang Y, Peloquin CE, Dubreuil M, Roddy E, Lu N, Neogi T, et al. Sleep apnea and the risk of incident gout: a population-based, body mass index-matched cohort study. Arthritis Rheumatol 2015;67:3298-302.

4. Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Comorbidities in patients with gout prior to and following diagnosis: case-control study. Ann Rheum Dis 2016;75:210-217.

5. Clarson LE, Hider SL, Belcher J, Heneghan C, Roddy E, Mallen CD. Increased risk of vascular disease associated with gout: a retrospective, matched cohort study in the UK Clinical Practice Research Datalink. Ann Rheum Dis 2015;74:642-647.

6. Kramer HJ, Choi HK, Atkinson K, Stampfer M, Curhan GC. The association between gout and nephrolithiasis in men: The Health Professionals' Follow-Up Study. Kidney Int 2003;64:1022-6.

7. Sultan AA, Mallen C, Hayward R, Muller S, Whittle R, Hotston M et al. Gout and subsequent erectile dysfunction: a population-based cohort study from England. Arthritis Res Ther 2017;19:123.

8. Choi HK, Atkinson K, Karlson EW, Curhan G. Obesity, weight change, hypertension, diuretic use, and risk of gout in men: the health professionals follow-up study. Arch Intern Med 2005;165:742-8.

9. Roughley MJ, Belcher J, Mallen CD, Roddy E. Gout and risk of chronic kidney disease and nephrolithiasis: meta-analysis of observational studies. Arthritis Res Ther 2015;17:90.

10. Choi HK, Soriano LC, Zhang Y, Rodriguez LA. Antihypertensive drugs and risk of incident gout among patients with hypertension: population based case-control study. BMJ 2012;344:d8190.

11. 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 Rheum 2007;15:109-15.

12. Richette P, Clerson P, Perissin L, Flipo RM, Bardin T. Revisiting comorbidities in gout: a cluster analysis. Ann Rheum Dis 2013;74:142-147.

13. Chandratre P, Mallen C, Richardson J, Rome K, Bailey J, Gill R 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 Disord. 2012;13:219.

14. IDF Consensus Worldside Definition of the Metabolic Syndrome. International Diabetes Federation, 2006.

15. Ferguson E, Cox T. Exploratory factor analysis: A users' guide. Int J Select Assess 1993;1:84-84.

16. Ward JH. Hierarchical grouping to optimize an objective function. *J Am Stat Assoc* 1963;58.236-244.

17. IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.

18. Roddy E, Muller S, Rome K, Chandratre P, Hider SL, Richardson J et al. Foot problems in people with gout in primary care: baseline findings from a prospective cohort study. J Foot Ankle Res 2015;8:31.

19. Dehlin M, Ekstrom EH, Petzold M, Strömberg U, Telg G, Jacobsson LT. Factors associated with initiation and persistence of urate-lowering therapy. Arthritis Res Ther 2017;19:6.

20. Clarson LE, Hider SL, Belcher J, Roddy E, Mallen CD. Factors Influencing Allopurinol Initiation in Primary Care. Ann Fam Med 2017;15:557-560.

21. Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Eligibility for and prescription of urate-lowering treatment in patients with incident gout in England. JAMA 2014;312:2684-6.

22. Richette P, Poitou C, Manivet P, Denis J, Bouillot JL, Clément K et al. Weight Loss, Xanthine Oxidase, and Serum Urate Levels: A Prospective Longitudinal Study of Obese Patients. Arthritis Care Res (Hoboken). 2016;68:1036-42.

23. Latourte A, Bardin T, Clerson P, Ea HK, Flipo RM, Richette P. Dyslipidemia, Alcohol Consumption and Obesity are the Main Factors Associated with Poor Control of Urate Levels in Patients Receiving Urate-Lowering Therapy. Arthritis Care Res (Hoboken). 2017 Aug 22. doi: 10.1002/acr.23347.

24. Choi HK, Soriano LC, Zhang Y, Rodriguez LA. Antihypertensive drugs and risk of incident gout among patients with hypertension: population based case-control study. BMJ 2012;344:d8190.

~~22~~25. Roddy E, Zhang W, Doherty M. Concordance of the management of chronic gout in a UK primary-care population with the EULAR gout recommendation. Ann Rheum Dis 2007;66:1311–55.

26~~23~~. Roddy E, Mallen CD, Hider SL, Jordan KP. Prescription and comorbidity screening following consultation for acute gout in primary care. Rheumatology (Oxford) 2010;49:105-11.

Table 1: Demographic, gout, and healthcare use ~~and alcohol consumption~~ characteristics of the ~~whole~~ cohort ~~providing consent to medical record review~~ (n=1079) and the four comorbidity clusters

	All (n=1079)	Cluster 1 (n=197)	Cluster 2 (n=393)	Cluster 3 (n=296)	Cluster 4 (n=193)
Demographics					
Male gender	909 (84)	135 (69)	350 (89)	256 (86)	168 (87)
Age, mean years (SD)	65.5 (12.5)	73.2 (11.0)	58.3 (12.3)	69.9 (9.1)	65.4 (10.6)
BMI, mean (SD)	29.2 (5.1)	28.9 (5.3)	28.6 (4.7)	29.1 (5.0)	30.4 (5.5)
History of gout					
Age at diagnosis, mean (SD)	53.3 (15.8)	63.4 (16.6)	47.0 (13.6)	55.4 (15.2)	53.3 (14.4)
Duration of gout, median (IQR)	8.0 (2-18)	4 (2-14)	7 (2-18)	11 (4-22)	9 (3-20)
Number of gout attacks in last 12 months 0 1-2 ≥3	361 (35) 381 (37) 285 (28)	53 (30) 69 (38) 58 (32)	131 (34) 146 (39) 102 (27)	107 (38) 96 (34) 77 (28)	70 (37) 70 (37) 48 (26)
Oligo/polyarticular attacks	399 (39)	68 (35)	145 (37)	114 (39)	72 (37)
Tophi	25 (2)	7 (4)	6 (2)	2 (1)	1 (1)
Renal calculi	9 (1)	0 (0)	6 (2)	2 (1)	1 (1)
Healthcare use Total number of consultations, Median (IQR)	14 (4-28)	19 (1-35)	7 (1-15)	23 (14-39)	14 (6-23)
Alcohol consumption					
Daily	259 (24)	42 (22)	102 (26)	65 (22)	50 (26)
Weekly	460 (43)	70 (36)	186 (48)	118 (40)	86 (45)
Monthly	106 (10)	19 (10)	33 (8)	32 (11)	22 (11)
Never/special occasions	242 (23)	62 (32)	68 (18)	78 (27)	34 (18)
>4 glasses wine per week	69 (6)	10 (5)	33 (8)	13 (4)	13 (7)
>7 pints of beer per week	266 (25)	19 (10)	132 (34)	49 (17)	66 (34)
>14 shots of spirits per week	29 (3)	6 (3)	6 (2)	8 (3)	9 (5)

Values are n (%) unless otherwise stated. SD standard deviation; IQR interquartile range

Table 2: Comorbidities and medications use among the ~~whole~~ cohort ~~providing consent to medical record review~~ (n=1079) and the four clusters

	All (n=1079)	Cluster 1 (n=197)	Cluster 2 (n=393)	Cluster 3 (n=296)	Cluster 4 (n=193)
Comorbidity					
Obesity[a]	358 (35)	57 (29)	116 (30)	100 (34)	85 (44)
Hypertension	432 (40)	95 (48)	0 (0)	144 (49)	193 (100)
Diabetes mellitus	175 (16)	1 (1)	0 (0)	147 (50)	27 (14)
Hyperlipidaemia	106 (10)	0 (0)	0(0)	106 (36)	0(0)
Metabolic syndrome[b]	181 (17)	31 (16)	0 (0)	91 (31)	59 (31)
Liver disorders	2 (<0.5)	0 (0)	1 (<0.5)	1 (<0.5)	0 (0)
Coronary heart disease	157 (15)	4 (2)	0 (0)	153 (52)	0 (0)
Heart failure	27 (3)	13 (7)	0 (0)	14 (5)	0 (0)
Chronic kidney disease stage ≥3 (eGFR<60ml/min)	318 (30)	192 (97)	0 (0)	126 (43)	0 (0)
Stage 3 (eGFR 30-59ml/min)	263 (25)	156 (79)	0 (0)	107 (36)	0 (0)
Stage 4/5 (eGFR<30ml/min)	55 (5)	36 (18)	0 (0)	19 (6)	0(0)
Cancer	34 (3)	9 (5)	10 (3)	13 (4)	2 (1)
Medications					
NSAIDs	634 (60)	96 (49)	250 (64)	172 (58)	116 (60)
Prednisolone	152 (14)	40 (20)	47 (12)	51 (17)	14 (7)
Colchicine	345 (32)	84 (43)	113 (29)	96 (32)	52 (27)
Allopurinol	646 (60)	110 (56)	218 (55)	202 (68)	116 (60)
Aspirin	282 (26)	63 (32)	36 (9)	152 (51)	31 (16)
Lipid-lowering drugs[c]	628 (58)	134 (68)	133 (34)	256 (86)	105 (54)
Diuretics	286 (27)	97 (49)	28 (7)	110 (37)	51 (26)
Losartan	55 (5)	13 (7)	5 (1)	21 (7)	16 (8)
Non-losartan ARB	118 (11)	30 (15)	8 (2)	56 (19)	24 (12)
Beta-blockers	297 (28)	79 (40)	34 (9)	138 (47)	46 (24)
ACE-inhibitors	413 (38)	109 (55)	46 (12)	154 (52)	104 (54)
Calcium channel blockers	276 (26)	69 (35)	26 (7)	93 (31)	88 (46)
Any non-losartan anti-hypertensive drugs	649 (60)	156 (79)	77 (20)	252 (85)	164 (85)

Values are n (%). [a]defined as body mass index ~~>~~ ≥30kg/m^2; [b] Defined as body mass index > 30kg/m^2 AND two of: hyperlipidaemia/lipid lowering therapy, hypertension or diabetes; [c] Other than fenofibrate; [d] Include non-losartan ARB, Beta-blockers, ACE-inhibitors, calcium channel blockers.

Table 3: Exploratory factor analysis

	Factor		
Comorbidity	**1**	**2**	**3**
Obesity	0.118	**0.771**	0.128
Hypertension	0.068	0.294	**0.680**
Diabetes	**0.471**	0.290	0.403
Hyperlipidaemia	**0.759**	0.087	-0.126
Coronary heart disease	**0.708**	-0.188	0.244
Heart failure	0.350	**-0.491**	0.270
Chronic kidney disease	0.114	-0.320	**0.725**

Factors with eigenvalue >1 are extracted; comorbidity's highest loading is highlighted