GOSPEL 4 - Patients with early onset gout develop earlier severe joint involvement and metabolic comorbid conditions

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Running head: GOSPEL 4 – Early onset gouts

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Abstract

Objective

Little is known of the clinical features and comorbidity profile of patients presenting with early onset gout (EOG) although international guidelines recommend their treatment rapidly after diagnosis. The objective of this study was to assess specific characteristics and comorbidities of patients suffering from gout having had an early onset.

Methods

Patients from a cross-sectional French national cohort ('GOSPEL'), having suffered their first gout flare before the age of 40 were included in the EOG group and compared to those with an onset after 40, the common gout group.

Results

A total of 120 patients, were included in the EOG group (aged 49.5 (±11.9) years) and 865 patients in the common gout group (aged 64.4 (±10.1) years). Patients with EOGmore often

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presented with a history of polyarticular flares ($p<0.01$), but had similar frequency of flares ($p=0.16$), gout arthropathy ($p=0.79$) and tophi ($p=0.53$). Prevalence of each item composing the metabolic syndrome did not differ between groups. In early onset patients, all cardiovascular comorbidities were diagnosed after gout onset. Greater age, low HDL and excessive alcohol intake were associated in multivariate analysis to the common gout group, while familial history of gout, longer urate lowering treatment, higher serum urate levels and the metabolic syndrome were associated to the early onset gout group.

Conclusion

Herein early onset gout patients developed slightly more severe joint involvement and earlier metabolic disorders than common gout patients.

Keywords: Gout; metabolic syndrome; early onset; chronic kidney disease

Significance and innovations

- Patients presenting with gout before the age of 40 develop earlier metabolic comorbidities
- Patients presenting with gout before the age of 40 develop earlier severe joint involvement
- Patients with early onset gout tend to preserve their renal function compared to those developing gout later on

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Gout is the most common inflammatory arthritis with a recent prevalence estimated at 0.9% in France and 3.9% in the United States (1, 2). The disease is triggered by monosodium urate (MSU) deposition after longstanding hyperuricaemia (3). Unsurprisingly, given the natural history of the disease, epidemiological studies agree that gout incidence increases with age until the age of 70 years and that onset before the forties is unusual (4, 5). Nonetheless, this observation does not apply to a significant proportion of patients; the prevalence of gout onset in adults between the age of 30 and 39 years reaching 1.3% in the United States (2).

This category of patients has been given specific attention by the recent European League Against Rheumatism (EULAR) and British Society of Rheumatology (BSR) guidelines that recommend a rapid initiation of urate lowering therapy (ULT) in patients diagnosed with gout before the age of 40 years (6, 7). Apart from few studies of Asian patients (8-10), little is known of the clinical features of patients presenting with early onset gout (EOG) in other populations, and particularly their comorbidity profile. Profiling these patients is a prerequisite to identifying patients and confirming the need for tailored management of gout in this population.

The GOSPEL cohort included a nation-wide representative population of patients treated for gout in outpatient practice in France (11). The objective of this GOSPEL 4 study was to compare the clinical presentation, evolution, disease characteristics and comorbidities of patients suffering from EOG to the general population of gout patients.

Methods

Study population

This study is part of the GOSPEL survey, completed in 2009, whose design and patient characteristics have been published elsewhere (11). This national cross-sectional

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epidemiologic survey included 1003 outpatients at least 18 years of age diagnosed by their own physician (private practice (PP) only) as being afflicted by gout. Patients having suffered from their first gout flare prior to the age of 40 were included in the early EOG group and compared to those with onset after 40 (common gout (CG) group).

Patients' clinical features, gout history, comorbidities and treatments prescribed were recorded by physicians (general practitioners (GPs) and PP rheumatologists) at the end of the baseline visit. Particularly, time from the first manifestations of gout was noted as well as time from/to the diagnosis of comorbid conditions. Items of the metabolic syndrome were defined as follows using the latest accepted definition: obesity (elevated waist circumference above 94 cm for men and 80 cm for women), elevated blood pressure (BP) (systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg or on-going anti-hypertensive therapy), elevated triglycerides (triglycerides ≥150 mg/dL or treatment), low HDL-c (HDL-c ≤ 40 mg/dL in men and ≤ 50 mg/dL in women or treatment), hyperglycaemia (≥100 mg/dL or drug treatment for elevated glucose)(12). Prevalence of the metabolic syndrome was secondarily calculated by the investigators and defined by the presence of at least 3 items of the metabolic syndrome, whether they had been looked for or not (12).

Creatinine clearance estimated by the Cockroft and Gault formula gave an estimation of the glomerular filtration rate (GFR). Only significant moderate or worse chronic kidney diseases (CKD) were considered (13, 14). Stage 2 CKD was not determined given that there was no research for proteinuria, renal imaging, or kidney histology findings. Stage 3 CKD was defined as a moderate alteration in eGFR between 30 and 60 mL/min, stage 4 CKD expressed a severe decrease in eGFR between 15 and 30 mL/min, and stage 5 CKD relates to kidney failure with eGFR below 15 mL/min(13).

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Statistical analysis

All statistical analyses were performed using R version 3.4. Qualitative variables were described as numbers (%) of each response modality; the number of missing data was recorded. Quantitative variables were described as mean ± standard deviation (SD), semi-quantitative variables as median [inter-quartile interval], and number of missing data. The two groups were compared on all variables. For quantitative and semi-quantitative variables, the Student test was used for normal data and the nonparametric Mann-Whitney test otherwise. Qualitative variables were assessed using the Chi2 or exact Fisher test as appropriate.

Multivariate analysis was then applied in order to identify significant associations of the variables with the EOG/CG groups. Using patients with all data available (no missing values), a binary logistic regression model was fitted with the variables exhibiting p-values lower than 0.2 in the bivariate analysis (group comparison). Selection of variables by an automatic step-by-step method based on the Akaike information criterion (AIC) was used. Adjusted odds ratios and 95% confidence intervals were presented.

Since the sample of patients without any missing value (379/985) was insufficiently representative of the whole study population, a multivariate analysis including a multiple imputation strategy using chained equations (MICE) was implemented. The hypothesis that the process generating missing data is *Missing At Random* (MAR) was considered. The Mice R package was used with five imputations for each missing data. Five "imputed" samples were obtained. The binary logistic model with automatic variable selection was fitted on each sample and pooled odds ratios and 95% confidence interval were computed.

In order to observe the influence of missing data imputation on the estimation model, the results obtained with the complete cases and those obtained using multiple imputations were compared.

All statistical tests were two-sided and P values were considered significant when equal to or less than 0.05.

Results

Bivariate analysis

The age of the first gout flare was known for 985 of the 1003 patients (98.2%) composing the GOSPEL cohort. Out of the 985 patients, 120 (12.2%) were included in the EOG group and were 49.5 (±11.9) years old at time of the study whereas the 865 patients of the CG group were aged 64.4 (±10.1) years ($p<0.0001$) (Table 1). Age of gout symptom onset is detailed in Figure 1.

Clinical presentation suggested disease to be more severe in the EOG group as compared to patients with CG. There was a significant greater proportion of patients having experienced other arthritis than the first metatarsophalangeal joint (MTP) in the EOG group (53.8%) than in the CG group (40.5%)($p<0.01$). Furthermore, more patients of the EOG group versus the CG group had significantly experienced polyarticular flare. Disease activity was similar between groups regarding the past year's number of flares although a lower proportion of patients reached the serum urate (SU) target of below 6.0 mg/dL in the EOG group (19.1% versus 29.8% ($p<0.05$))(15). Severity of the disease was also similar for both arthropathy and clinically palpable tophi (Table 1).

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Patients from the EOG group reported their general health as being better (75.8% good, 23.3% fair and 0.8% poor) compared to those of the CG group ((63.4% good, 32.6% fair and 4.0% poor) (p=0.02). On a scale of 0 (none) to 100 (worse), gout tended to have a greater impact on the mood of patients of the EOG group of 41.3 (± 33.0) compared to 33.6 (±27.7) (p=0.09) in the CG group. Using a similar scale, all patients considered that gout had a negative impact on their social life at a level of 29.3 (± 30.9) in the EOG group versus 27.9 (±25.5) (p=0.52) in the CG group.

Regarding comorbidities, a greater proportion of patients in the CG group were suffering from moderate to severe chronic kidney disease (CKD) (estimated glomerular filtration rate (eGFR) below 60ml/min, Cockcroft-Gault formula), as 130/611 (21.3%) with available estimated glomerular filtration rate (eGFR) had CKD 3 or 4 in the CG group compared to 5/79 (6.3%) in the EOG group (p<0.01). The metabolic syndrome was significantly more prevalent in the CG group (554/865 (64.0%) patients) than in the EOG group (64/120 (53.3%) patients) (p<0.05). When considering each individual item of the metabolic syndrome, prevalence of each item was not significantly different between groups when they were measured (Table 1).

Time from the physician-diagnosis of cardiovascular complications to the first symptoms of gout was significantly different between groups. Gout preceded all cardiovascular events in the EOG group contrary to the CG group where all events were diagnosed at about the same time as gout.

Multivariate analysis

Multivariate analysis was performed using 18 variables exhibiting p-values lower than 0.2 in the bivariate analysis (group comparison). Only 12 variables were retained in at least one of the reduced model (no missing value model and models on the 5 imputed samples). Odd

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ratios (OR) for these 12 variables are presented for the no missing value only model and pooled OR for the multiple imputations model in Table 2. Overall, 40 patients of the EOG group and 339 patients of the CG had all data available. In the EOG group, the data was available as follows: excessive alcohol consumption (117/120), the metabolic syndrome (70/120), SU level (113/120). Greater age, low HDL and excessive alcohol intake were associated to the CG group, while familial history of gout, longer ULT treatment, higher SU levels and the metabolic syndrome were associated to the EOG group. Association of the EOG group with the metabolic syndrome was highly significant in the model including only patients having all data available with an OR of 7.04 [1.4-47.03], but significance was lost in the model using multiple imputations (1.87 [0.91-3.83] (p=0.09)). Conversely, excessive alcohol intake was not significantly associated to the CG group in the model including only patients with all data available (p=0.07), but was significant in the multiple imputation model (p=0.02). Prevalence of the metabolic syndrome was strongly associated with excessive alcohol consumption (p=0.009). Excessive alcohol consumption was frequently a missing value (19% of all missing data) and its imputed values had therefore a high influence on the significance of the association of the metabolic syndrome.

Discussion

This study provides an assessment of the profile of patients suffering from evolved early onset gout in France. Despite longer disease duration at time of study, these EOG patients presented with fewer renal and physician-identified cardiovascular comorbidities than the common profile of gouty patients followed in clinical practice. Yet, notwithstanding their younger age, patients with EOG presented with joint involvement as severe as patients 15-years older with the so-called classical profile. Even more concerning, the 50-year-old

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patients shared the same prevalence of diabetes mellitus and individual items of the metabolic syndrome as 65-year-old classical gout patients. Whereas the first signs of gout usually appear around the diagnosis of other metabolic comorbidities, in our early onset patients, gout preceded most other comorbidities. These results further suggest the existence of a window of opportunity for the rapid treatment of patients developing gout before the age of 40 advocated by EULAR relying on expert opinion (6).

Knowledge of gout genetics is growing and it is now known that gene polymorphisms participate in the disease progression. Genetics can account for the development of EOG even in the absence of associated risk factors such as the metabolic syndrome, excessive alcohol intake, drugs or CKD (16). The probability is high that such EOG patients developed gout largely because of genetic polymorphisms given the fact that they were not particularly heavy drinkers, had on average better renal function, took fewer diuretics and had less prevalent metabolic syndrome features. Genetic mutations, such as partial HPRT deficiency (17), or mostly uric acid transportosome mutations (18), are not routinely tested in clinical practice for gout management, and the weight of genetics in the development of gout in younger patients cannot be thoroughly addressed by this study. High frequencies of ABCG2 proteins have been found in a recent retrospective cohort study from China, without difference between EOG and CG (10). For Matsuo *et al*, common dysfunction of ABCG2 is a major cause of EOG and its detection might serve to improve earlier prevention and therapy for high-risk individuals (19). However, the higher prevalence of known familial history of gout in the EOG group further supports the hypothesis of a strong underlying genetic basis.

Missing data accounts for discrepancies in performance of the metabolic syndrome and excessive alcohol consumption in the 2 multivariate models. Multiple imputations models consider multiple scenarios in their construction, which widens the range of the OR, providing a possible explanation of why the metabolic syndrome performs differently in the 2

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models as 42% of values had to be imputed (versus 29% in the CG group). On the contrary, given the very small number of missing data for alcohol consumption, the range of the OR was reduced in the multiple imputation model because the sample was increased and few imputations needed to be performed.

Our study suggests that patients with EOG develop earlier metabolic conditions and, despite longer disease durations, tend to preserve their kidney function. A Taiwanese case-controlled study of very early gout onset (before the age of 20) suggested that despite their higher body mass index, very EOG tophaceous patients had on average lower lipid and fasting glucose levels when compared to middle-aged onset gout patients. Data from the Chinese cohort studied by Zhang *et al.* had overall a better cardiovascular profile and particularly had much lower prevalence of metabolic syndrome (10). Furthermore, Asian patients with very EOG also had preserved renal functions despite longer disease duration in both Asian populations (8, 20). Our multivariate analysis has also shown that the lipid profile of EOG was better than the one of the CG group, as low-HDL was significantly associated with the latter in all models tested. Yet, the smaller than expected difference between the groups concerning the prevalence of the metabolic syndrome in bivariate analysis was surprising given the age difference (21). Multivariate analysis has confirmed that suspicion: once adjusted on age, the metabolic syndrome was significantly associated to the EOG group in the model using only patients with all available data. This result was only a trend in the model using multiple imputations due to the association of excessive alcohol consumption with the CG group. Indeed, given the strong association of the metabolic syndrome and excessive alcohol intake, some of the crude higher prevalence of the metabolic syndrome in the CG group was related to higher alcohol consumption (22-24). Furthermore, bivariate analysis and the model using multiple imputations provided worse case scenarios of the link between EOG and the metabolic syndrome because missing data which was in proportion

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more important in the EOG group was considered as an absence of item of the metabolic syndrome, with a higher risk to underestimate its prevalence in the EOG group. The model including only patients with all available data certainly provided the best case scenario and the strength of the link between EOG and the metabolic syndrome probably lies in between.

Although gout has been shown to be implicated in the progression of CKD, our results support the hypothesis that renal function is less impacted by early than late gout (10, 25). Taking this into account, specific attention should be given to metabolic conditions in EOG patients, more so than the preservation of kidney function that seems less at stake.

Overall, our study suggests that disease activity and severity of the joint involvement of EOG are comparable to those of later-on onset gouts, as confirmed by multivariate analysis. This is surprising given prior data found in the literature. Yu *et al.* performed a retrospective analysis of 1,079 Taiwanese gout patients showing a younger age of onset than usual (average age of 41.6 years) and far shorter disease duration than our EOG group (4.2 years). Patients presented with more severe gout and recurrent yearly flares (75.9% of patients presented with at least three flares per year), higher SU levels (10.3 mg/dL) and almost as many tophi (16.8%) compared to our cohort (9). Abhishek *et al.* tried to identify factors associated with recurrent gout flares among untreated gout patients and found that high SU levels and long disease duration predict recurrent flares, but with poor performance (26). Higher SU levels in the Taiwanese patients probably explain the more recurrent flares and early tophi than in our GOSPEL cohort EOG group. The three-fold longer disease duration in the EOG group led to similar disease severity in these patients, who on average had not yet reached their fifties, than in gout patients with the classical profile, who are on average 15 years older. This finding further supports the recent recommendation made by the EULAR and the BSR to treat early patients presenting with early gout, not only to prevent aggravation of comorbidities but also the outcome of severe chronic joint lesions (6, 7).

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We acknowledge that this study has some limitations. Patients included in the GOSPEL cohort were considered as having gout by their physician but were not crystal-proven. A large majority of patients however presented with at least 6 items of the 1977 ACR criteria and their proportion was similar between groups (27). The new 2015 ACR/EULAR criteria could not be applied retrospectively (28). Secondly, not all patients had recent biological tests which may have impaired to some extent assessment of SU levels, dyslipidemia and hyperglycaemia but this could be corrected by multivariate analysis using the multiple imputation model. Using the multiple imputation model is a robust and stringent statistical analysis which fully takes into account the missing data. In this model, variables that remain significant are reliable. Thirdly, recollection of the date of the first symptoms of gout and diagnosis of comorbidities is subject to imprecision.

In routine practice, patients with EOG present during their evolution with slightly different joint involvement and similar disease severity than the more common middle-age onset gout patients. Despite younger age on average, they present with similar prevalence of diabetes mellitus and metabolic conditions as their older counterparts but benefit from rather preserved renal function. Given these early joint and metabolic complications, this study advocates for an early management of patients with early onset gouts.

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Tables and Figures

Characteristics (number of patients with available data)	Early onset gout (n =120)	Common gout (n = 865)	p
Demographics			
Age (years) (n=985)	49.5 (±11.9)	64.4 (±10.1)	<0.0001
Age at gout onset (years) (n=985)	32.8 (±5.7)	57.2 (±10.9)	<0.0001
Gout duration (years) (n=985)	16.2 (±13.1)	6.9 (±6.7)	<0.0001
Male	96,7%	86,6%	0.08
Known family history of gout (n=980)	38.1%	16.7%	<0.0001
Renal stone (n=974)	8.5%	3.6%	<0.05
Excessive alcool consumption (n=793)	41.8%	50.8%	0.12
Daily alcohol consumption (g/day) (n=793)	27.7 ± 27.2	31.8 ± 31.1	0.1
Daily consumption of sugar-sweetened beverages (n=799)	35.4%	26.6%	0.09
Body mass index (kg/m^2)(n=979)	28.7 (± 4.0)	28.3 (±4.1)	0.16
Clinical tophi (n=985)	17.5%	19.9%	0.54
Treatment			
Ongoing ULT (n=973)	68.9%	67.9%	0.91
ULT (allopurinol) duration (years) (n=970)	11.3 (±10.2)	6.6 (±6.0)	<0.001
SU level at ULT initiation (mg/dL) (n=943)	8.86 (± 1.52)	8.54 (± 1.19)	<0.05
Last SU level (mg/dL) (n=802)	6.97 (±1.70)	6.77 (±1.97)	0.14
Last SU level below 6.0mg/dL (n=802)	19.1%	29.8%	<0.05
Joint disease			
Gout arthropathy (n=985)	22.5%	23.6%	0.79
Number of flares per year (n=985)	2.14 (±1.75)	1.93 (±1.49)	0.06
At least 2 flares per year (n=985)	96.7%	92.7%	0.16
At least one polyarticular attack (n=956)	49.6%	34.8%	<0.01
Arthritis other than 1^{st} MTP joint (n=954)	53.8%	40.5%	<0.01
Comorbidities			
eGFR below 60ml/min (n=690)	6.3%	21.3%	<0.01
Ischemic heart disease (n=973)	3.4%	9.4%	<0.05
Physician-indentified dyslipidemia (n=975)	36.4%	48.9%	<0.01
Physician-identified hypertension (n=979)	30.8%	57.8%	<0.0001
Cerebrovascular accident (n=970)	1.7%	3.3%	0.57
Physician-identified diabetes mellitus (n=973)	12%	15.5%	0.38
Diuretics use (n=985)	9.2%	23.5%	<0.0001
Metabolic syndrome (n=985)	53.3%	64.0%	<0.05
High blood pressure (n=984)	85%	91%	0.06

Hyperglycaemia/T2D (n=691)	61.8%	60.5%	0.93
Abdominal obesity (n=899)	82.1%	82.7%	0.99
Low HDL-c (n=662)	57.6%	67 .4%	0.14
Hypertriglyceridemia (n=696)	77 .6%	81.6%	0.53

Table 1: Characteristics of the early onset and common gout groups.

SU: serum urate level; ULT: urate lowering therapy; MTP: metatarsophalangeal; eGFR: Estimated glomerular filtration rate (estimated by the Cockroft-Gault formula); T2D: type 2 diabetes

The metabolic syndrome was defined as the presence of at least 3 of the 5 following items, all item with missing data were considered negative. Abdominal obesity was defined by elevated waist circumference above 94 cm for men and 80 cm for women), high blood pressure was defined by systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg, or on-going anti-hypertensive therapy, hypertriglyceridemia defined by triglycerides ≥150mg/dL or treatment, low HDL-c defined by HDL-c ≤ 40mg/dL in men and ≤ 50 mg/dL in women or treatment, hyperglycaemia defined by fasting glucose ≥100 mg/dL or drug treatment for elevated glucose.

Statistical significance defined by $p<0.05$.

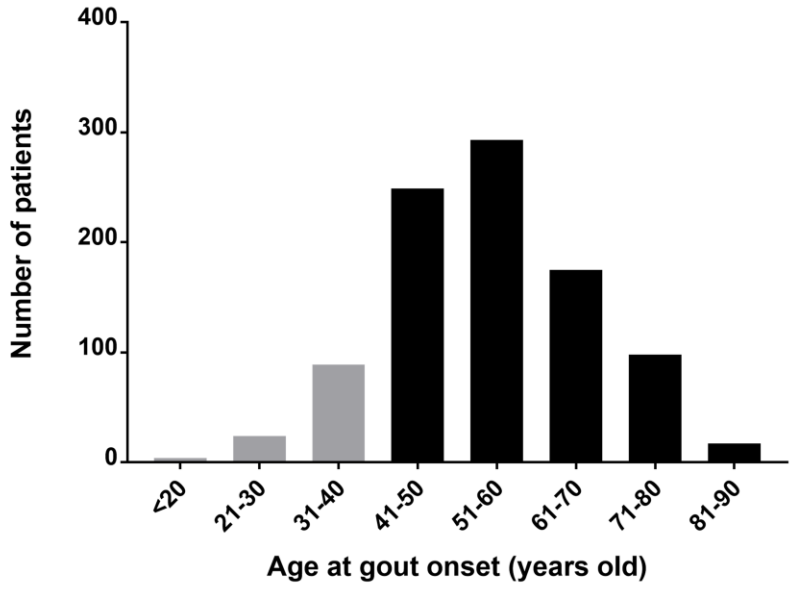
Variables	No missing value model (N=379)			Multiple imputations model (N=985)		
	adjusted OR	**CI 95%**	**p-value**	**adjusted OR**	**CI 95%**	**p-value**
Age	**0.83**	**[0.78-0.88]**	**<0.0001**	**0.8**	**[0.77-0.83]**	**<0.0001**
Known familial history of gout	**3.12**	**[1.28-7.69]**	**0.01**	**2.33**	**[1.31-4.13]**	**0.004**
Renal stone	1.25	[0.09-8.22]	0.84	2.82	[0.86-9.18]	0.08
Excessive alcool consumption	0.41	[0.16-1.06]	0.068	**0.51**	**[0.29-0.9]**	**0.02**
ULT (allopurinol) duration (years)	**1.2**	**[1.13-1.29]**	**<0.0001**	**1.23**	**[1.17-1.29]**	**<0.0001**
Last SUA level (mg/dL)	**1.006**	**[1.002-1.01]**	**0.009**	**1.006**	**[1.003-1.01]**	**0.0006**
At least one polyarticular attack	1.12	[0.39-3.5]	0.84	1.59	[0.86-2.95]	0.14
Arthritis other than 1st MTP joint	1.34	[0.55-3.29]	0.51	1.64	[0.93-2.9]	0.08
Physician-diagnosed dyslipidemia	3.17	[0.8-14.43]	0.12	2.15	[0.81-5.68]	0.12
Diuretics use	0.41	[0.09-1.39]	0.19	0.82	[0.35-1.89]	0.64
Metabolic syndrome	**7.04**	**[1.4-47.03]**	**0.03**	1.87	[0.91-3.83]	0.09
Low HDL	**0.2**	**[0.04-0.87]**	**0.04**	**0.26**	**[0.09-0.75]**	**0.01**

Table 2 : Variables associated with early onset gout group taking common gout group as reference.

Multivariate analyses of odd ratios (OR) and confidence intervals (CI) of explanatory variables using a model integrating patients with all available values only (no missing value model) and a model using multiple imputations for missing values. SU: serum urate level; ULT: urate lowering therapy; MTP: metatarsophalangeal. Statistical significance defined by $p<0.05$.

Figure Legends

Figure 1: Age of gout onset: distribution of study participants.



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