Comorbidity and its impact on the course of gout and COVID-19

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Introduction. Comorbid diseases significantly exacerbate gout burden, represent an even more elevated risk of hospitalization and mortality rates owing to the coronavirus disease 2019 (COVID-19) than gout itself.

Objectives. To evaluate the influence of the modified Rheumatic Disease Comorbidity Index (mRDCI) on the clinical course of gout and COVID-19.

Methods. Using data from 136 male participants with gout, we distributed the cohort according to values of the mRDCI as follows: 0 – without comorbidities, 1-2 – low comorbidity index (CI), 3-4 – moderate CI and ≥5 – high CI. "Treat-to-target" approach for gout, the association of mRDCI with the clinical course of gout, lipid metabolism, and severity of COVID-19 were analyzed.

Results. According to mRDCI scores, almost every second gout patient (45.6%) had moderate CI, every fifth (19.1%) – high CI, and 14.7% – low CI. Greater mRDCI was associated with the higher severity of COVID-19 (p=0.003), limited physical functioning (r=0.5, p<0.001), higher body mass index (r=0.63, p<0.001), hyperuricemia (r=0.37, p<0.001), increased low–density lipoprotein cholesterol (LDL–C) (r=0.38, p<0.001), higher gout activity (r=0.4, p<0.001), more frequent acute flares in the preceding year (r=0.39, p<0.001), number of tophi (r=0.31, p<0.001), longer duration of gout (r=0.34, p<0.001), reduced glomerular filtration rate (r=−0.39, p<0.001), and daily excretion of uric acid (UA) (r=−0.28, p=0.001). The target level of serum UA was achieved in 22.1%. The majority of patients were not controlled for LDL-C (83.7%), blood pressure (75.5%), and glucose (69.44%) in the cohort with dyslipidemia, hypertension, and diabetes respectively.

Conclusion. The high prevalence of comorbidities in gout patients was associated with the severity of COVID-19. Three patterns of comorbidity predictors have been identified: disease-related, dysmetabolic, and unmodifiable.

Keywords: gout, hyperuricemia, uric acid, goals, prevalence, risk, comorbidity, COVID-19

Особливості перебігу подагри та COVID-19 в умовах коморбідності

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Вступ. Коморбідні захворювання значно збільшують тягар подагри, становлять вищий ризик госпіталізації та смертності внаслідок пандемії коронавірусної хвороби 2019 (COVID-19 ніж сама подагра.

Мета. Охарактеризувати вплив модифікованого коморбідного індексу для ревматологічних захворювань (mRDCI) на клінічний перебіг подагри та COVID-19.

Методи дослідження. Згідно показників mRDCI (0, 1-2, 3-4 чи ≥5) розподілено 136 чоловіків з подагрою на 4 квартилі: пацієнти без коморбідності, з низьким, середнім та високим коморбідним індексом відповідно. Оцінювали "лікування до цілі" подагри, асоціацію mRDCI з клінічним перебігом подагри, ліпідним обміном та перебігом COVID-19.

Результати. Згідно mRDCI майже кожен другий пацієнт з подагрою (45.6%) мав середній, кожен п'ятий (19.1%) – високий, а 14.7% – низький ІК. Вищий mRDCI асоціюється із гіршим ступенем тяжкості COVID-19 (p=0.003), нищим фізичним функціонуванням (r=0.5, p<0.001), більшим індексом маси тіла (r=0.63, p<0.001), гіперурекемією (r=0.37, p<0.001), *підвищенням холестерину ліпопротеїнів низької щільності* (ХС ЛПНЩ) (r=0.38, p<0.001), вищою активністю подагри (r=0.4, p<0.001), *більшою частотою загострень за останній рік* (r=0.39, p<0.001), кількістю тофусів (r=0.31, p<0.001), тривалістю подагри (r=0.34, p<0.001), зменшенням швидкості клубочкової фільтрації (r=−0.39, p<0.001) та добової екскреції сечової кислоти (СК) (r=−0.28, p=0.001). Цільовий рівень СК досягли лише 22.1% хворих. Більшість пацієнтів з дисліпідемією, артеріальною гіпертензією та цукровим діабетом не були контрольованими за рівнем ХС ЛПНЩ (83.7%), артеріального тиску (75.5%) та глюкози (69.4%) відповідно.

Висновки. Висока поширеність коморбідних станів у пацієнтів з подагрою асоціюється з важкістю перебігу COVID-19. Встановлено три патерни предикторів коморбідності: хворобопов'язаний, дисметаболічний та немодифікований.

Ключові слова: подагра, гіперурикемія, сечова кислота, ціль, поширеність, ризик, коморбідність, COVID-19.

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Introduction

According to the latest data, the prevalence of gout ranges from 0.02% to 6.8% with the incidence of 0.58–2.89 per 1,000 person-years. [1]. In Europe it affects between 0.9% and 2.5% of the population [2, 3, 4], while in the United States – 3.9% [5] and 6.24% - in Taiwan [6]. The prevalence and incidence of gout is constantly increasing worldwide. Researchers from the US have reported that its incidence almost doubled in 2009-2010 as compared with 1989-1992 [7].

Evidence suggests that increasing gout prevalence is asscociated with excess direct healthcare cost. On average, the additional annual cost of treating gout is more than $ 3,000 per patient, with increased expences for those having frequent exacerbations of gout or tophi [8].

Other studies have shown that the mechanism of the monosodium urate crystal-related gout inflammatory reaction involves pro-inflammatory factors (interleukin (IL) -1β, IL-8 and IL-17, NLRP3 inflammatory mass and tumor necrosis factor alpha (TNF-α), as well as anti-inflammatory factors (IL -10 and IL-37) [9]. Theoretically, this may be the cause of an enhanced immune response to severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2).

Although gout is a potentially curable condition, its management remains suboptimal [2]. Untreated or poorly controlled gout can lead to impairments to quality of life and productivity [10]. Gout and hyperuricemia are strongly associated with hypertension, chronic kidney disease, obesity, diabetes, nephrolithiasis, myocardial infarction, heart failure, stroke. The prevalence of comorbidities was 3 to 33-fold higher as compared with those with serum uric acid levels below 4 mg/dL [11]. Gout patients with SUA>0.56 mmol/l and tophi have a higher association with cardiovascular diseases, cancer, and infectious diseases-related mortality compared to the general population [12]. The majority of these comorbidities (hypertension, chronic heart disease, kidney, lung, liver disease, stroke, obesity, diabetes), as well as male gender and age, are established the risk factors for death from coronavirus disease 2019 (COVID-19) [13].

Comorbid conditions in rheumatic and musculoskeletal diseases (RMDs) increases morbidity and mortality, increase disease activity, limit drug use and are associated with higher hospitalization and mortality rates owing to the 2019 coronavirus pandemic (COVID-19). In this context, comorbidities are associated with a higher risk in RMDs population, than the RMDs themselves. Reducing these risks requires proper identification and management of comorbid diseases, especially in the light the COVID-19 pandemic [14].

The issue of COVID-19 course and outcome of as well as the guidelines for gout control during SARS-CoV-2 infection remain relevant today. Given the prevalence of comorbidities, the risk for unfavourable outcome of COVID-19 is probably the highest in gout population among the patients with RMDs. The American College of Rheumatology and European League Against Rheumatism (ACR/EULAR) have provided guidelines for the management of RMDs in the context of SARS-CoV-2, which do not include gout. This was probably due to the fact that gout was underrepresented in publications describing the course and consequences of COVID-19 [15].

That is why the purpose of this study was to assess the prevalence of comorbid conditions among gout patients in Ukraine, to identify unfavourable prognostic factors, as well as to determine whether the higher gout-specifically modified Rheumatic Diseases Comorbidity Index (mRDCI) is a risk factor for the more severe clinical course of gout and coronavirus disease 2019 (COVID-19).

Materials and Methods

The study population included 136 male patients with gout, aged 50.49 (49.41 - 51.58) years who were observed in the Rheumatology Department of Ternopil University Hospital during September 2018 – August 2021. Inclusion criteria included age of 38-65 years, gout duration of three and more years, obtained informed consent from a patient. Exclusion criteria included female gender, asymptomatic hyperuricemia, psoriasis, stage IV – V chronic kidney disease, alcohol abuse.

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The study procedures complied with the Helsinki Declaration of the World Medical Association on the ethical principles of scientific medical research with human participation (1964-2008). This study was approved by the Human Ethics Committee at the Ternopil National Medical University (N. 54, August 27, 2019). Each patient signed the written informed consent before participating in the study.

Research design
1. Assessment of gout (disease duration, the number of gout flares within the past 12 months, stage of disease, presence of tophi, tophi number, previous urate-lowering therapy and its effectiveness, gout activity, physical functioning, the adherence to a hypopurine diet, patient's awareness of the target SUA level, SUA level, and daily urine uric acid excretion).
2. Assessment of Comorbidities.
3. Indexation of the mRDCI.
4. Distribution of the gout cohort according to the values of the mRDCI into the following established quartiles: 0 – without comorbidities (quartile 1), 1-2 – low comorbidity index (CI) (quartile 2), 3-4 – moderate CI (quartile 3) and ≥5 – high CI (quartile 4).
5. Estimation the relative risk of the mRDCI in the study population.
6. Previous "treat-to-target"of gout, hypertension, dyslipidemia, and diabetes mellitus.
7. Analysis of the severity of COVID-19 depending on the mRDCI distribution in the gout cohort.

The diagnosis of gout was confirmed according to 2015 Gout Classification Criteria: ACR/EULAR 2015 [16]. Comorbidities were established based on the medical records and laboratory tests (lipid profile) prior to or on admission to the Rheumatology Department. Body mass index (BMI) was used for diagnosis of obesity according to the World Health Organization classification [17]. Glomerular filtration rate (GFR) was estimated by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [18].

Gout activity was calculated according to the Gout Activity Score [19]. Physical functioning was assessed with the Health Assessment Questionnaire (HAQ) disability index [20]. The Patient Health Questionnaire-9 (PHQ-9) was used to confirm depression (PHQ-9≥10) [21].

Indexation of the comorbid status of each patient was calculated base on the mRDCI [22, 23]. We distributed the cohort according to the values of the mRDCI into the following established quartiles: 0 – without comorbidities, 1-2 – low comorbidity index (CI), 3-4 – moderate CI and ≥5 – high CI.

Gout patients were interviewed about the number of gout flares within the past 12 months, their adherence to a hypopurine diet, their knowledge of the target SUA level, and smoking status.

Preliminary effectiveness of treatment of hypertension, dyslipidemia, diabetes mellitus was assessed by the target levels of blood pressure (BP) according to 2020 International Society of Hypertension global hypertension practice guidelines [24], low-density lipoprotein cholesterol by 2019 European Society of Cardiology and European Atherosclerosis Society Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk [25] and glucose/glycosylated hemoglobin according to 2021 American Diabetes Association Standards of Medical Care in Diabetes [26] respectively.

During the second visit to the rheumatologist, the above-mentioned study group was assessed for the fact of SARS-CoV-2 infection, the severity of COVID-19 (as of August 30, 2021). COVID-19 diagnosis was confirmed with a SARS-CoV-2 positive polymerase chain reaction test of a nasopharyngeal swabs. COVID-19 disease severity was assessed according to the World Health Organization Guidelines [27].

All statistical analyses were conducted using Statistical analysis software STATISTICA 10.0 (StatSoft. Inc.). Continuous variables were expressed as mean (M) and 95% confidence interval (95% CI) for parametric data or as median (Me) and its interquartile range (IQR) (25th percentile - 75th percentile) for nonparametric data. Categorical variables were expressed as frequencies and percentages (%). Comparison of qualitative indicators was

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carried out using the Pearson Chi-square test (χ^2) between groups. Spearman correlation analysis between the two variables with non-normal distribution or Pearson correlation analysis between the two variables with normal distribution were used to determine the relationships between the indicators. Simple linear regression analysis was performed to estimate the relative risk of the mRDCI in the study population. A p value less than 0.05 was considered statistically significant.

Results

The baseline data of the study patients (n = 136) are shown in Table 1. We examined a group of gout patients who were Caucasian males (100%). Age (mean (95 % CI) and disease duration (Me (IQR) were 50.49 (49.41 - 51.58) years and 8.5 (5 – 15) years, respectively.

Our study has established the prevalence of comorbid diseases in gout patients represented by cardiovascular, dysmetabolic, gastrointestinal, renal, and pulmonary patterns (Fig. 1).

The results of our study highlight prevalence of comorbidities based on the mRDCI (median (IQR) 3 (2-4). Almost every second patient (45.6%) had moderate CI, every fifth (19.1%) – high CI, every seventh (14.7%) – low CI.

The current findings provide further insight into the impact the comorbidities have on the clinical course of gout (Figs. 2, 3). The analysis comorbidities in gout allowed to identify three patterns of predictors: unmodifiable (older age), disease-related (duration of gout, increase of acute flares in the preceding year, tophi number, poor physical functioning, high disease activity, hyperuricemia, and decreased daily uric acid excretion) and dysmetabolic (obesity, hypertriglyceridemia, hypercholesterolemia, elevated LDL cholesterol, and decreased GFR).

The simple linear regression analysis of the relationship between the mRDCI and clinical or laboratory data showed that the mRDCI score has a significant prognostic effect on them (p≤0.001) (Table 2) and confirmed the above-mentioned associations.

Patients' characteristics	Value	Patients' characteristics	Value
Gout patients, n (%)	136 (100)	Age, years (M (95 % CI)	50.49 (49.41 – 51.58)
Stage of disease, n (%) Acute stage Intermission Chronic stage	 25 (18.38) 11 (8.08) 100 (73.52)	**Place of residence,** n (%) Urban Rural	 77 (56.62) 59 (43.38)
Disease duration, years (Me (IQR)	8.5 (5 – 15)	**Smoking status, n** (%) Never Current Ex	 64 (47.06) 31 (22.79) 41 (30.15)
Acute flares in the preceding year (Me (IQR)	4 (1.5 – 6)	**HAQ–DI** (M (95 % CI)	0.68 (0.62 – 0.74)
VAS patient global, cm (Me (IQR)	5 (3 – 7)	**eGFR, ml/min/1,73 м²** (Me (IQR)	94 (79 – 106)
Presence of tophi, n (%)	53 (38.97)	**BMI, kg/m²** (Me (IQR)	31.45 (28.35 – 35.4)
Tophi number (Me (IQR)	0 (0 – 14)	**TC, mmol/l** (Me (IQR)	5.67 (5.01 – 6.15)
GAS$_{3\ step-c}$ (Me (IQR)	4.86 (4.02 – 7.34)	**HDL–C, mmol/l** (Me (IQR)	1.06 (0.91 – 1.31)
SUA level, mg/dl (Me (IQR)	8.2 (6.72 – 9.16)	**LDL–C, mmol/l** (Me (IQR)	3.5 (2.91 – 4.06)
SUA <6 mg/dl, n (%)	30 (22.06)	**Triglycerides, mmol/l** (Me (IQR)	2.18 (1.33 – 3.21)
Daily urine UA excretion, mmol/24h (Me (IQR)	2.94 (1.93 – 3.6)	**mRDCI (0–12)** (Me (IQR)	3 (2-4)

Note. M (95 % CI): mean and 95% confidence interval; Me (IQR): median and interquartile range; HAQ–DI: Health Assessment Questionnaire Disability Index; VAS: visual analog scale (0–10 cm); eGFR: estimated glomerular filtration rate; BMI: body mass index; TC: total cholesterol; GAS 3 step-c: Gout Activity Score 3 step-c; HDL–C: high-density lipoprotein cholesterol; SUA: serum uric acid; LDL–C: low-density lipoprotein cholesterol; UA: uric acid; mRDCI: gout-specifically modified Rheumatic Disease Comorbidity Index.

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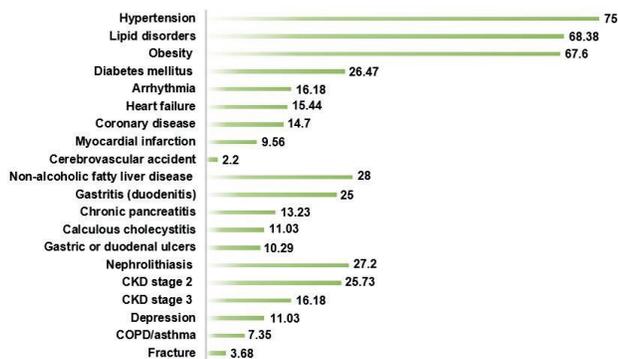Original research: Clinical sciences

Figure 1. Percentage prevalence of comorbid pathology in gout patients (n=136).

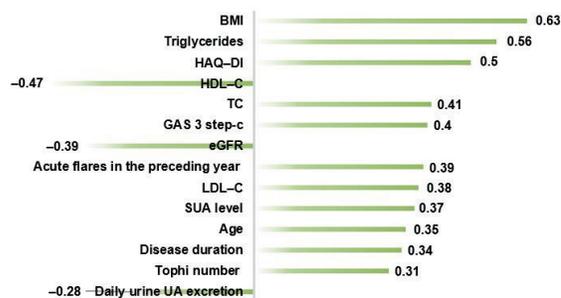CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease.

Figure 2. Pearson correlation between the mRDCI and age or the HAQ–DI in patients with gout. Spearman correlation between the mRDCI and other baseline characteristics of gout cohort (clinical course of gout, purine metabolism, and cardiometabolic risk factors). Correlation coefficients are demonstrated at the end of each bar. All correlations were statistically significant (p≤0.001).
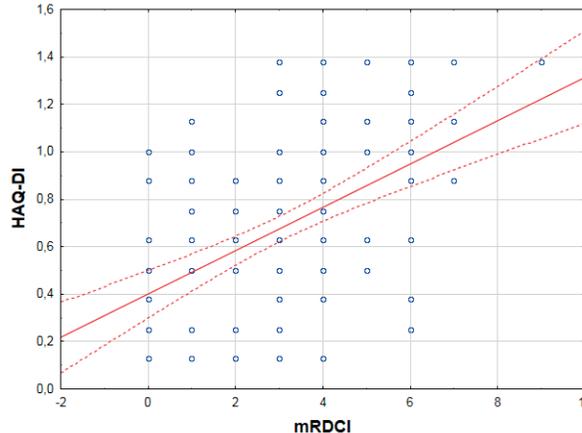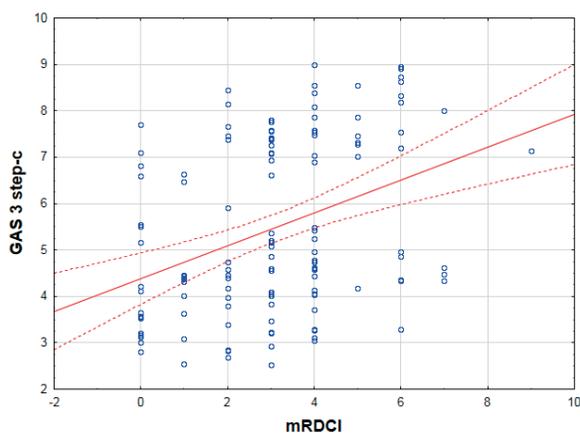

Figure 3. Scatterplots of the mRDCI depending on the $GAS_{3\,step-c}$ and HAQ-DI in gout patients.

SUA goal level achievement rates in Ukrainian patients with gout are still poor, with 66.91% receiving urate-lowering therapy (ULT) (62.64% – allopurinol and 37.36% – febuxostat), with 28.68% following hypopurine diet, and with 22.06% of patients achieving SUA targets. The proportion of participants who achieved the serum urate targets was the highest among patients without comorbidities and the lowest among patients with high mRDIC score (65% in the group without comorbidity, versus 25% for low mRDCI, 14.52% for moderate mRDCI, and 3.85% for high mRDCI, p<0.001). Furthermore, only 8.82% of patients were aware of their treatment goal (SUA <6 mg/dl).

Regarding "treat-to-target" comorbidities, the majority of patients did not have well-controlled LDL-C (n=77, 83.7%), blood pressure (n=77, 75.5%), and glucose/glycosylated hemoglobin values (n=25, 69.4%) in the subgroup with dyslipidemia (n=92), hypertension (n=102), and diabetes (n=36), respectively.

COVID-19 was confirmed in 30.88% of patients with gout (March 1, 2020 to August 30, 2021). Most gout patients infected with SARS-CoV-2 were classified to have moderate disease (40.48%), almost every third (28.57%) patient had mild illness, while 21.43% of patients had severe disease, and 9.52% had critical disease. Greater mRDCI was found to be a reliable predictor of more severe clinical course in COVID-19 ($\chi2=24.82$; p=0.003) (Table 3).

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Table 2

**The simple linear regression analysis results
of mRDCI on clinical and laboratory characteristics of gout patients**

Risk Factor	β (SE)	B (SE)	R^2	P-value
Age	0.374 (0.08)	1.209 (0.259)	0.133	p<0.001
Disease duration	0.361 (0.08)	1.097 (0.245)	0.131	p<0.001
Acute flares in preceding 1 year	0.386 (0.08)	0.55 (0.11)	0.149	p<0.001
VAS patient global	0.362 (0.08)	0.4 (0.089)	0.131	p<0.001
Tophi number	0.348 (0.081)	1.62 (0.377)	0.12	p<0.001
GAS $_{3\ step-c}$	0.371 (0.08)	0.356(0.076)	0.138	p<0.001
HAQ–DI	0.497 (0.075)	0.091 (0.014)	0.25	p<0.001
SUA level	0.38 (0.079)	0.306 (0.064)	0.144	p<0.001
Daily urinary excretion of uric acid	-0.299 (0.082)	-0.169 (0.046)	0.089	p=0.001
eGFR	-0.502 (0.075)	-5.788 (0.861)	0.25	p<0.001
BMI	0.619 (0.068)	1.456 (0.159)	0.383	p<0.001
TC	0.357 (0.081)	0.189 (0.043)	0.127	p<0.001
HDL–C	-0.475 (0.076)	-0.064 (0.01)	0.226	p<0.001
LDL–C	0.353 (0.081)	0.149 (0.034)	0.1248	p<0.001
Triglycerides	0.552 (0.072)	0.378 (0.049)	0.31	p<0.001

Note. ß (SE): standardized regression coefficient with Standard Error. B (SE): non-standardized coefficient of regression with Standard Error

Table 3

**Gout, COVID-19 diagnosis, and COVID-19 severity depending
on the mRDCI quartile distribution**

	Value, n (%)	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p-value[c]
COVID-19 diagnosis	42 (30.88)	2 (10)	5 (17.86)	16 (25.81)	19 (73.08)	p<0.001
COVID-19 severity						p=0.003
Mild	12 (28.57)	2 (100)	4 (80)	6 (37.5)	0(0)	
Moderate	17 (40.48)	0 (0)	1 (20)	8 (50)	8 (42.1)	
Severe	9 (21.43)	0 (0)	0 (0)	2 (12.5)	7 (36.84)	
Critical	4 (9.52)	0 (0)	0 (0)	0 (0)	4 (21.05)	

Note. c - *Pearson Chi-Quadrat-Test*.

Discussion

Our results demonstrate that gout patients are often have associated comorbidities. The prevalence of hypertension [7, 11, 12, 28], dyslipidemia [7, 11, 12, 28], obesity [7, 11, 23], and nephrolithiasis [11] was high in our study.

We confirmed the previously demonstrated by Spaetgens et al. [23] relationship between the mRDCI and HAQ-DI (r=0.42 vs r=0.5), mRCDI and age (r=0.33 vs r=0.35). Only the correlation between the mRDCI and disease duration (r=−0.26 vs r=0.34) was slightly different [23]. Our study provides further insight into the association of the mRDCI with impaired purine (SUA, daily excretion of UA) and lipid metabolism (levels of TC, LDL-C,

HDL-C, triglycerides), clinical course of gout (frequency of acute gout flares within the past 12 months), and decreased renal function.

The findings of this study confirm that gout is an undertreated disease in Ukraine. Low rates of ULT prescriptions and SUA goal attainment have also been described in other countries. Although ULT was recommended for 80.7% of gout patients, <50% of the population achieved the SUA goal in Japan [29]. In the UK, among gout patients, only 48.48% were treated with ULT and among them 37.63% took ULT. Moreover, less than 20% of incident gout cohort received ULT within 6 months and 27.3% within 12 months of diagnosis [2]. There is a lack of knowledge about the target

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values of SUA among gout patients who receive ULT. Another study has shown that only 14% of patients knew their SUA goal [30].

In the context of COVID-19 in patients with ≥ 1 comorbid condition, the results of our study are consistent with the findings of Osibogun et al. [31]: about half of the COVID-19 infected individuals exhibit a mild illness, every third have moderate and less than 10% have severe illness. Different mechanisms of the immune response depending on the severity of COVID-19 are described [32], as well the U-shaped association between uricemia and risk of adverse outcomes in the SARS Cov-2 infected individuals [33].

We recognize several limitations of our study. First, the relatively small sample size was assesed (n=136). Second, participants were recruited from the inpatient Rheumatology Department of the University Hospital, and likely had the higher severity rates of gout. The majority of patients included in our study have a poorer comorbidity status compared with outpatient gout population [34, 35]. This is why our findings need to be further demonstrated among all gout population. Third, we did not rate adherence to ULT, which is low in clinical practice (17–83.5%) [36]. Fourth, the SUA testing was not estimated. According to our literature review, it remains extremely low. In the United States, SUA measurement was conducted nearly once per year for gout patients with tophi but less than once a year for those with acute flare or chronic gout without tophi [37]. This is one of the leading issues in the gout control, as the gout is not only an acute transient arthritis, but a chronic inflammatory disease [38]. Overall, continued administration of ULT with dose titration and regular SUA testing to achieve target SUA level ≤6 mg/dl, decrease not only frequent flares of gout, but also the prevalence of co-

morbidities among gout population [39]. The evidence that gout impacts on the pathogenesis of their comorbidities requires the need for the optimal gout control [40].

One of the limitations of the mRDCI is that it does not count all possible and frequent comorbidities (dyslipidemia, nephrolithiasis), although include the main cardiovascular, gastrointestinal diseases, obesity, kidney disease, diabetes, depression, lung disease, fracture and cancer. However, the mRDCI is validated for gout population [23].

To sum up, these findings emphasize that a high prevalence of comorbid conditions was associated with the severity of COVID-19 in gout patients. An assessment of the mRDCI allowed to establish three patterns of comorbidity predictors: disease-related (longer duration of gout, greater frequency of gout attacks in the preceding year, disease activity, hyperuricemia, tophi number, and poorer physical functioning), dysmetabolic (higher body mass index, hypertriglyceridemia, hypercholesterolemia, increased LDL-C, decreased HDL-C and renal function), and unmodifiable (older age). A high proportion of uncontrolled hyperuricemia, hypertension, dyslipidemia, glycemia hypothetically indicates suboptimal management of both gout and its comorbidities in Ukraine. A comprehensive, multidisciplinary approach is needed for these population. A more in-depth study is necessary to find a more conclusive explanation for the role of purine metabolism in the pathogenesis of comorbidities and the course of COVID-19.

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