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Original Article

Comparative analysis of clinical characteristics of gout patients

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Abstract

Aim: Given the documented rise in the incidence and prevalence of gout over the past decade, this study aims to comparatively assess patients of different ages affected by gout in Romania and the Republic of Moldova.

Material and methods: This cross-sectional observational study selectively included 490 patients with gout treated in the Republic of Moldova and Romania

Results: In Romania, the study included 15 women (6.1%) and 230 men (93.9%) (mean age 52.24±1.18 years). The mean age of gout onset in these patients was 42.5±0.89 years. In the Republic of Moldova, 26 women (10.6%) and 219 men (89.4%) were included (mean age 49.2±1.05 years), with mean age of gout onset 47.6±0.52 years. Of Romanian patients, 29 (11.8%) had chronic intermittent gout with a primary attack, 42 (17.2%) had repeated attacks, and 174 (71%) had chronic tophaceous gout. In the Republic of Moldova, there were 11 (4.5%) patients with chronic intermittent gout and a primary attack, 28 (11.5%) patients with repeated attacks, and 206 (84%) patients with chronic tophaceous gout. Hereditary predisposition was observed in six (2.5%) patients in Romania and nine (3.8%) patients in the Republic of Moldova, most frequently among family members such as fathers, brothers, and uncles.

Conclusions: The study reveals similarities and differences between patient's from Romania and the Republic of Moldova in terms of prevalence, clinical evolution and hereditary predisposition of gout, underlining the need for a tailor-made approach in the management of this disease.

Keywords

gout, comorbidities, Romania, Republic of Moldova

Introduction

The term "gout" is still used today, and the basic concept of urate crystal deposition—which is essential to understanding the disease's pathogenicity and what causes inflammation in the joints—is gaining increasing attention.[1] Recent studies have made significant progress in our understanding of the epidemiology of gout by examining the prevalence of gout, its risk factors, and the relationship between hyperuricemia and gout, including comorbidities and mortality **(Fig. 1)**.[2-4]

Globally, there has been a notable rise in gout-related deaths and injuries throughout the past three decades. Despite the lack of significant differences in prevalence between Moldova and Romania, the Republic of Moldova has a lower incidence of gout (0.028%-0.038%) than Romania (0.031%-0.043%).[3] Gout patients have a significantly higher risk of cardiovascular death (OR=1.56, 95% CI, 1.50%-1.63%) than healthy individuals, making cardiovascular disease the primary cause of death in this population.[4] Patients with gout also died from kidney illness, infections, diabetes, lung diseases, digestive disorders, and other conditions far more frequently than those in the control groups.[5]

Krishnan and his colleagues have demonstrated that patients with gout are at a significantly higher risk of myocardial infarction and cardiovascular mortality than those without gout. This increased risk was not observed in individuals with asymptomatic hyperuricemia (HU).[6]

Similar results were recently reported by Kuo and co-authors in a longitudinal study in Taiwan patients. In a retrospective study conducted in a group of veterinarians in the USA, it was shown that allopurinol reduction therapy was associated with significant benefits in terms of survival of patients with HU (OR=0.78, 95% CI, 0.67%-0.91%).[7]

Co-morbidities such as dyslipidemia, obesity, insulin resistance, type 2 diabetes mellitus, arterial hypertension, ischemic heart disease, chronic heart failure, and chronic renal disease are the main factors adversely affecting quality of life and in some cases the prognosis of patients suffering from gout.[8]

One of the determinants of high prevalence of metabolic syndrome in gout patients is a close link between metabolic disorders and HU.[9] Our study has demonstrated the influence of hyperuricemia on the development of atherosclerosis in the coronary and carotid arteries resulting in an increased incidence of acute myocardial infarction, stroke, and vascular dementia.[10] It has been established that uric acid has the capacity to directly stimulate the renin-angiotensin system, inhibit vascular nitric oxide synthesis, stimulate smooth muscle cell proliferation in the walls of vessels, and cause kidney damage. Collectively, these factors contribute to the development of hypertension. Increases in uric acid levels are also associated with hypertriglyceridemia and disorders of carbohydrate metabolism.[11]

Hence, gout or HU can be considered as independent risk factors for cardiovascular disease.[12] In addition to hyperuricemia, another predictor of increased prevalence of cardiovascular pathology in patients with gout is inflammation, an issue that has been studied recently.[13] Among inflammatory markers, special attention was given to high-sensitivity C-reactive protein (hsCRP).[14] hsCRP not only plays an important role in diagnosing joint inflammatory diseases, but has been shown to be the most sensitive marker for cardiovascular risk compared to

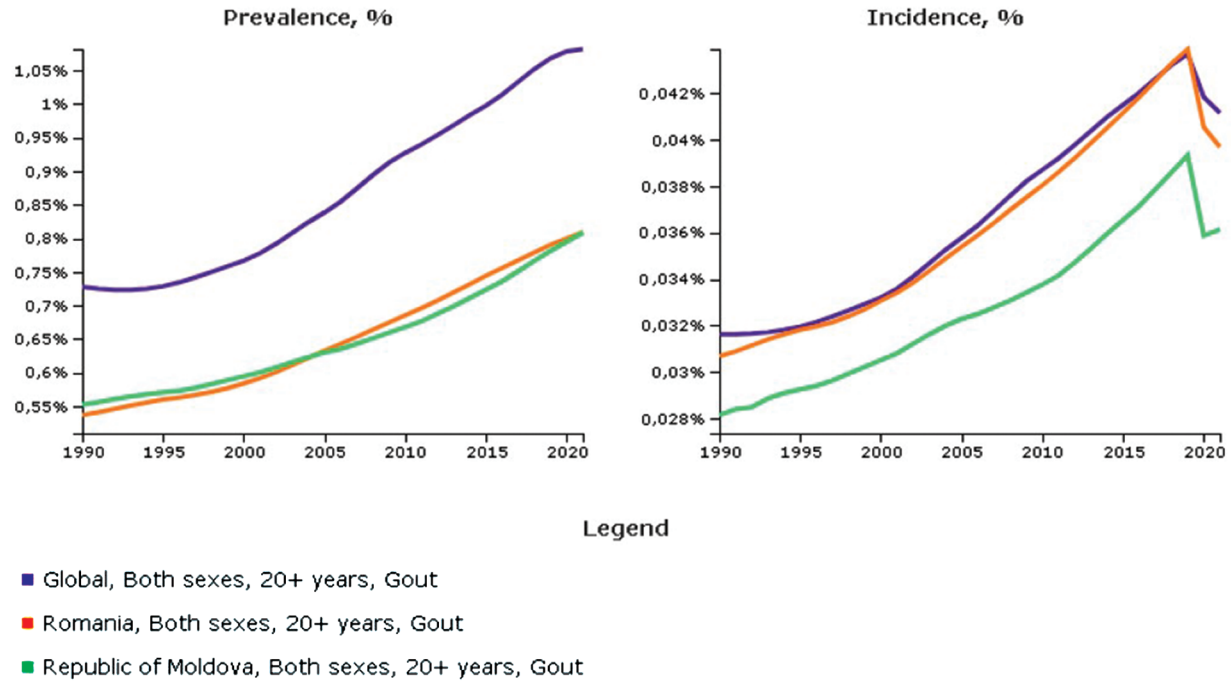

Figure 1. Cause of death or injury around the globe, in Romania, and in the Republic of Moldova.[2]

homocysteine and lipoproteins.[15] Many studies showed a strong correlation between hsCRP levels and factors such as body mass index (BMI), waist circumference, and lipid parameters.[10,12,14,16]

Aim

The aim of the present study was to make a comparative assessment of patients of different ages affected by gout in Romania and the Republic of Moldova, with a view to analyzing similarities and differences in prevalence, treatment, and disease progression in the two countries. A specific objective was to compare the prevalence of concomitant medications (antihypertensives, lipid-lowering agents, antidiabetic drugs, NSAIDs, colchicine, allopurinol, and febuxostat) in the two national cohorts.

Material and methods

This cross-sectional, observational, selective study included 245 gout patients treated at the Department of Nephrology, Rheumatology, and Arthrology at the Republican Clinical Hospital in Moldova from 2010 to 2016. The patients were analyzed for established comorbidities. For comparison, 245 patients with gout treated in the Clinic Hospital (Cluj-Napoca, Romania) were included in the Department of Rheumatology Iuliu Haţieganu University of Medicine and Pharmacy (Cluj-Napoca) between 2006 and 2010.

An important premise of the study was the use of very rigorous criteria for selecting patients with gout, which excluded the possibility of errors in diagnosis. In specifying the disease, diagnostic criteria accepted by the American College of Rheumatology (ACR) were taken into account. The criteria for inclusion of patients in the study were age for patients of both sexes over 18 years, diagnosis of gout according to ACR criteria (2015), and presence of informed consent. The criteria for exclusion of patients in the study were oncologic pathology and lack of informed consent.

Results

The study included 245 gout patients [15 (6.1%) women and 230 (93.9%) men] from Romania, and 245 gout patients [26 (10.6%) women and 219 (89.4%) men] from the Republic of Moldova **(Table 1)**.

In both cases, the predominance of male patients is evident, which aligns with the data of other authors in different countries of the world.

The mean age of gout patients in Romania was 52.24±1.18 years and the mean age of onset for gout was 42.5±0.89 years **(Table 2)**. The mean age of gout patients from Moldova was 49.2±1.05 years and the mean age of onset for gout was 47.6±0.52 years **(Table 2)**.

The distribution of gout patients from Romania by clinical form of gout was as follows: Intermittent chronic gout: 29 patients (11.8%), primary attack: 42 patients (17.2%), and repeated attack and chronic tophaceous gout: 174 patients (71%) **(Table 3)**.

The distribution of gout patients from the Republic of Moldova by clinical form of gout was as follows: intermittent chronic gout, 11 patients (4.5%); primary attack, 28 patients (11.5%); repeated attack; and chronic tophaceous gout, 206 patients (84%) **(Table 3)**.

According to the distribution of patients by clinical form, chronic tophaceous gout predominates in Romania and the Republic of Moldova, followed by chronic intermittent gout.

Hereditary predisposition was found in 6 (2.5%) patients in Romania and 9 (3.8%) patients in the Republic of Moldova. Gout was most common among family members and parents: father, brother and uncle **(Table 4)**.

At the time of the primary examination, the majority of Romanian patients in the study (171, or 69.8%) had acute joint attacks, with a mean duration of 15.3±0.98 days, compared to only 136 (55.5%) patients in the Republic of Moldova, with a median duration of 12.4±0.69 days. The frequency of acute relapses was comparable for the two countries, ranging from one attack to two years to one attack per month. In our study, we observed that the longer the disease had been present, the more severe the deterio-

Table 1. Distribution of gout patients from Romania and the Republic of Moldova by sex

Sex / Country	Women			Men		
	n	%	95% CI	n	%	95% CI
Romania	15	6.1	3.78-7.3	230	93.9	77.6-101.2
Republic of Moldova	26	10.6	8.8-12.1	219	89.4	81.4-96.7

CI: confidence interval; n: number of patients (absolute)

Table 2. Distribution of gout patients in Romania and Moldova by mean age and mean age of onset of gout

Age	Romania	Republic of Moldova	*p*
Mean age of patients, (years±SD)	52.24±1.18	49.2±1.05	0.0001
Mean gout onset age, (years±SD)	42.5±0.89	47.6±0.52	0.0001

p: Student's t-test; SD: standard deviation

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Table 3. Distribution of gout patients from Romania and Moldova by clinical form

Clinical form	Romania n (%)	Republic of Moldova n (%)	95% CI min	95% CI max	*p*
Chronic intermittent gout (with primary access)	29 (11.8)	11 (4.5)	2.87	17.8	0.4934
Chronic intermittent gout (with repeated access)	42 (17.2)	28 (11.5)	7.33	23.2	0.5150
Chronic tophaceous gout	174 (71)	206 (84)	41.1	97.3	0.0023

* $p<0.05$, n: number of patients (absolute); *p*: Student's t-test; CI: confidence interval

Table 4. Distribution of gout patients in Romania and the Republic of Moldova by hereditary predisposition

Parameters	Romania n (%)	Republic of Moldova n (%)	p
Hereditary predisposition (1st grade)	6 (2.5)	9 (3.8)	0.8936

* $p<0.05$, n: number of patients (absolute); p: Student's t-test

ration and the longer it took to occur.

To prevent pain and functional insufficiency from affecting the results, joint function was evaluated during the intercritical time. The findings were as follows: most patients in both countries showed signs of joint dysfunction: 155 (63.3%) in Romania and 149 (60.8%) in the Republic of Moldova. This was classified as functional class II, meaning they were functioning fully except for joint pain and stiffness.

Only 34 patients (13.9%) in Romania and 41 patients (16.7%) in Moldova had more advanced joint function insufficiency. Except during times of joint crisis, the remaining patients (56 patients, or 22.8% in Romania, and 55 patients, or 22.5% in the Republic of Moldova) did not exhibit any critical changes that were functionally active. These were categorized as Grade I because of a lack of common function.

We examined the provoking factors in the patients included in the study. Regarding alcohol usage, 21 (8.6%) of the Romanian patients said that they "do not consume alcohol," while the remainder 224 (91.4%) "admitted that they consume alcohol." Of those, 89% consume alcohol "on occasion," while only 11% "consume alcohol daily." In comparison, 18 (7.3%) of patients in the Republic of Moldova indicated they "do not consume alcohol," while the remainder 227 (92.6%) said they "admit they consume alcohol," with 82% saying they consume alcohol "on occasion" and only 18% saying they "consume daily."

Overweight and obesity (body mass index between 25 kg/m^2 and 29.9 kg/m^2, and BMI ≥30 kg/m^2, respectively) were observed with a comparable frequency in the patients of Romania and the Republic of Moldova (p=0.11). Administration of diuretics to gout patients was registered in 47 (19.2%) patients in Romania and 36 (14.7%) patients in the Republic of Moldova.

It is noteworthy that most of the study patients developed gout against an intact joint backg round (patients did not experience joint pain), but there were also patients developing gout against a background of a joint disorder, including:

1. Posttraumatic osteoarthritis – 66 (26.9%) patients in Romania and 52 (21.2%) in the Republic of Moldova,
2. Psoriatic arthritis – 19 (7.8%) patients in Romania and 31 (12.7%) patients in the Republic of Moldova,
3. Rheumatoid arthritis – 12 (4.9%) patients in Romania and 9 (3.7%) patients in the Republic of Moldova.

We analyzed the distribution of comorbidities in the gout groups in Romania and the Republic of Moldova **(Table 5)**.

Table 5. Distribution of comorbidities in the group of gout patients in Romania and the Republic of Moldova

Nosology	Romania	Republic of Moldova	*p*
Arterial hypertension, n (%)	197 (80.4)	195 (79.6)	0.8432
Osteoarthritis, n (%)	66 (26.9)	52 (21.2)	0.4760
Ischemic heart disease, n (%)	116 (47.3)	145 (59.2)	0.0558
Chronic tubulo-interstitial nephropathy, n (%)	103 (42.0)	118 (48.2)	0.3568
Dyslipidemia, n (%)	139 (56.7)	141 (57.6)	0.8793
Nephrolithiasis, n (%)	78 (31.8)	86 (35.1)	0.6558
Hepatic steatosis, n (%)	145 (59.2)	157 (64.1)	0.3822
Obesity, n (%)	155 (63.3)	160 (65.3)	0.7115
Type 2 diabetes mellitus, n (%)	69 (28.2)	57 (23.3)	0.5341
Psoriatic arthritis, n (%)	19 (7.8)	31 (12.7)	0.5923

n: number of patients (absolute); *p*: Student's t-test

We found that, among the analyzed comorbidities, arterial hypertension ranked first in both countries, affecting 197 (80.4%) patients in Romania and 195 (79.6%) patients in the Republic of Moldova (0.039, 0.8432). Obesity ranked second, affecting 155 (63.3%) in Romania and 160 (65.3%) in the Republic of Moldova (0.137, 0.7115). Hepatic steatosis was the third most prevalent comorbidity, affecting 145 (59.2%) patients in Romania and 157 (64.1%) in the Republic of Moldova (0.764, 0.3822). The other comorbidities were distributed differently by country, with a predominance in the Republic of Moldova **(Fig. 2)**.

We also compared the prevalence of concomitant medication use between cohorts. We based the assumed medication distributions on the prevalence of known comorbidities and standard gout management. For example, hypertension affects about 75% of gout patients, so most would be on antihypertensives. Similarly, diabetes affects about 16% of patients, so many would be on antidiabetic therapy. For acute gout, nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine are the recommended first-line therapies, so we assumed that nearly all patients would use NSAIDs at some point, and that many would use colchicine. Allopurinol is the preferred first-line urate-lowering drug, and febuxostat is reserved for patients who are intolerant to or refractory to allopurinol. These recommendations informed us of our assumptions about urate-lowering therapy use. Using these assumptions, we compared medication use between the cohorts, as shown in **Table 6**.

As shown in **Table 6**, antihypertensive and antidiabetic drug use did not significantly differ between the cohorts ($p>0.05$). However, lipid-lowering agent use was significantly higher in Romania (57.1%) than in Moldova (40.8%; $p<0.001$). Colchicine use was also significantly higher in Romania (36.7%) than in Moldova (24.5%; $p=0.004$). In contrast, allopurinol use was significantly higher in Romania (73.5% vs. 57.1%; $p<0.001$), whereas febuxostat

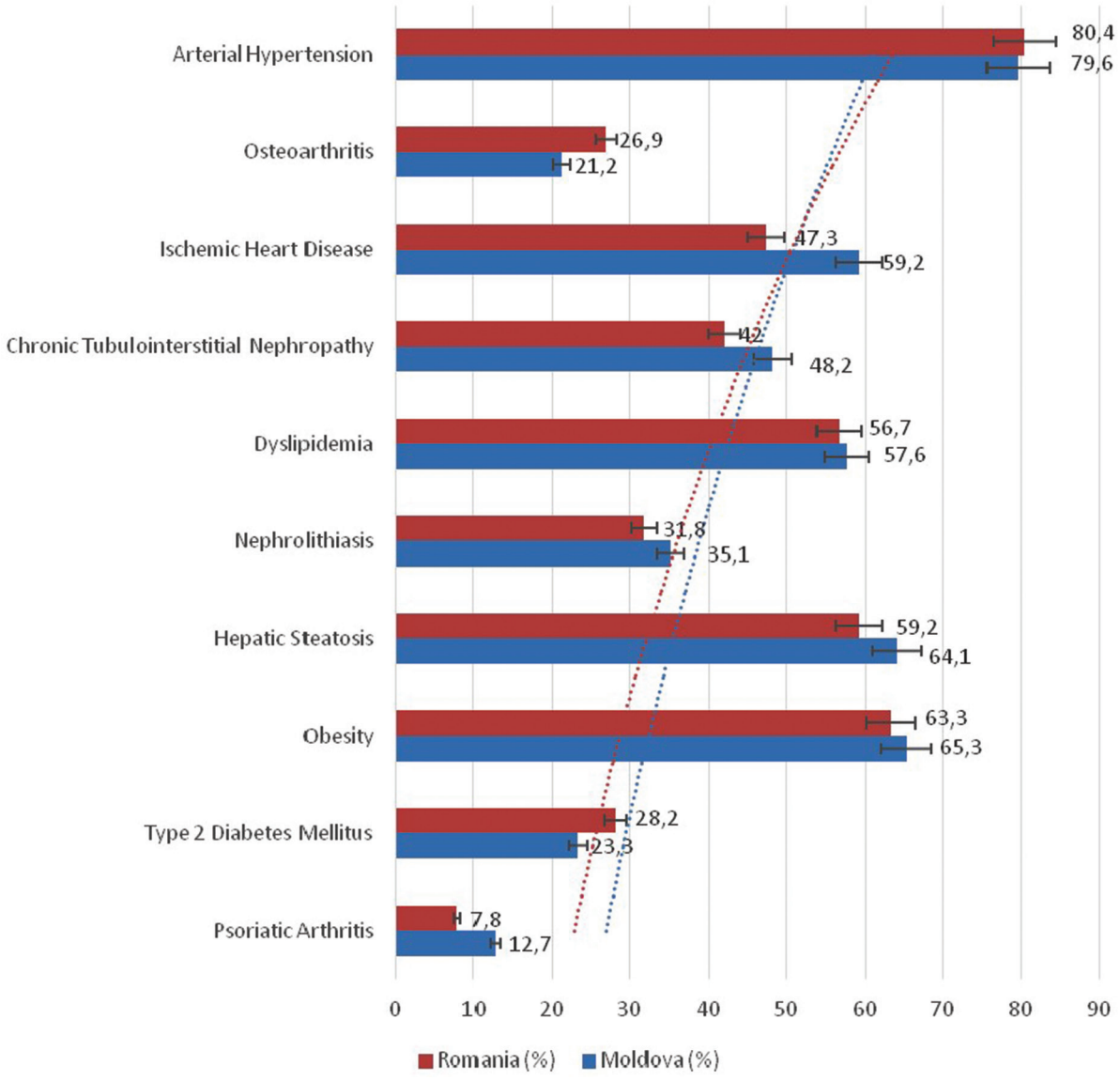

Figure 2. Frequency of comorbid pathologies in gout patients in Romania and the Republic of Moldova.

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Table 6. Distribution of concomitant medication use in gout patients (Romania vs. Republic of Moldova)

Medication	Romania n (%) (n=245)	Moldova n (%) (n=245)	*p*-value
Antihypertensives	190 (77.6%)	180 (73.5%)	0.34
Lipid-lowering agents	140 (57.1%)	100 (40.8%)	<0.001*
Antidiabetic drugs	70 (28.6%)	60 (24.5%)	0.36
NSAIDs	240 (98.0%)	235 (95.9%)	0.29
Colchicine	90 (36.7%)	60 (24.5%)	0.004*
Allopurinol	180 (73.5%)	140 (57.1%)	<0.001*
Febuxostat	30 (12.2%)	60 (24.5%)	<0.001*

*$p<0.05$, chi-square test.

was used more commonly in Moldova (24.5% vs. 12.2%; $p<0.001$). NSAID use was nearly universal in both groups, with no significant inter-country difference ($p>0.05$). These differences suggest regional variations in treatment practices: for instance, Romania's higher statin and allopurinol use may reflect first-line therapy preferences, while Moldova's higher febuxostat use indicates alternative urate-lowering strategies.

Discussions

Correctly identifying risk factors and implementing measures to correct them through adequate lifestyle changes is of the utmost importance in the prevention of many conditions. Specific prevention strategies and interventions must also be applied. Naturally, given the varying economic levels of different regions, the same risk factors may impact disease development differently depending on the regional context. Multiple studies have investigated gout triggers, which include hereditary and exogenous factors such as a diet rich in purines, excessive alcohol consumption, and the use of certain medications (e.g., diuretics and cyclosporine), as well as sedentary behavior.[17] Factors such as nationality, social status, education level, and rural residence were found not to significantly influence disease progression.[18] Epidemiological studies in various regions show that gout prevalence and incidence are mainly associated with the aforementioned factors, which are more prevalent in populations with sedentary lifestyles, an imbalanced diet, and alcohol consumption. Uric acid hypersecretion and renal excretion deficiency are also major pathophysiological elements that predispose one to gout, regardless of socio-economic background.

Examining gout patients in Chișinău, Republic of Moldova, and Cluj-Napoca, Romania, and their associated diseases, it was observed that the frequency of arterial hypertension was similar in both cities. This finding indicates a consistent association between gout and cardiovascular comorbidities, a topic frequently discussed in the literature. However, comorbidities such as osteoarthritis and type 2 diabetes mellitus are more prevalent among patients in Romania. This may suggest a greater influence of urban lifestyles or other region-specific socioeconomic factors. Conversely, nephrolithiasis associated with gout is more prevalent in patients in the Republic of Moldova, suggesting a higher incidence of renal impairment due to hyperuricemia in this population. These findings underscore the importance of a tailored approach to assessing and monitoring gout patients, considering the associated comorbidities and regional specifics of the disease. Gout remains a relevant medical problem in both Romania and the Republic of Moldova in the context of systemic chronic pathology, not only due to its increased prevalence, but also due to the wide spectrum of clinical manifestations and local specificities. These data underscore the need for personalized treatment approaches tailored to each patient's clinical profile, focusing on controlling trigger factors through specific interventions and managing associated comorbidities to optimize long-term outcomes.

Notably, analysis of medication usage revealed significant differences between countries: Romanian patients had higher rates of lipid-lowering medication use (57.1% vs. 40.8%) and allopurinol use (73.5% vs. 57.1%), while Moldovan patients had higher rates of febuxostat use (24.5% vs. 12.2%). These disparities likely reflect variations in treatment guidelines or drug availability. For instance, Romania's higher use of allopurinol (the primary urate-lowering therapy) suggests more rigorous urate management, whereas Moldova's greater use of febuxostat indicates alternative therapeutic strategies.

Conclusions

This comparative study reveals partially overlapping, yet distinct, gout profiles in Romania and the Republic of Moldova. The incidence and sex distribution are similar in both countries, though a statistically significant difference was observed in the mean age of diagnosis and clinical form distribution. Patients in the Republic of Moldova more frequently presented with chronic tophaceous gout (84% vs. 71%, $p=0.0023$), which suggests either delayed diagnosis or a more aggressive disease course. Hereditary predispo-

sition was documented in a small proportion of patients in both cohorts (2.5% in Romania and 3.8% in Moldova). However, these findings are limited by the self-reported nature of familial data, which does not allow for definitive conclusions regarding the genetic contribution.

The comorbidity analysis revealed a significant prevalence of cardiovascular and metabolic conditions in both countries, with arterial hypertension and obesity being the most common. There were no statistically significant intergroup differences for most comorbidities ($p>0.05$), suggesting that shared risk profiles are likely influenced by common dietary and lifestyle factors rather than disparities in the healthcare systems.

However, the higher frequency of nephrolithiasis and psoriatic arthritis among patients in Moldova warrants further investigation. Due to the cross-sectional design, though, no causal associations can be inferred. Incorporating medication data highlights the need for tailored gout management strategies in each country. These findings underscore the importance of harmonizing treatment practices and ensuring access to first-line therapies. Further studies should assess the impact of these pharmacotherapy differences on long-term gout outcomes.

In summary, the data support the need for gout management strategies adapted to different regions, emphasizing the early detection of chronic forms and the proactive identification of comorbidities. However, longitudinal and mechanistic studies are needed to validate the observed trends and better understand the causes of differences between countries.

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