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https://doi.org/10.31925/farmacia.2026.3.6 **ORIGINAL ARTICLE**

PREVALENCE OF HYPERURICEMIA AND THE EVIDENCE-BASED IMPACT FACTORS ON SERUM URIC ACID LEVELS

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Abstract

This cross-sectional health survey aimed to assess the prevalence of hyperuricemia and identify the pharmacological and anthropometric factors influencing serum uric acid (SUA) levels in a Romanian community pharmacy setting. Data were collected from 377 participants (aged 18–89) at two pharmacies in Călărași County. Measurements included SUA, blood pressure, fasting glucose, and BMI. Multivariable linear regression with multiple imputation was used to identify predictors of SUA levels. Hyperuricemia prevalence was 40.4% among participants with measurable levels. Potent diuretics, specifically indapamide and furosemide, were strongly associated with higher SUA levels ($\beta = 1.22$, $p < 0.001$). Height emerged as a significant independent predictor ($\beta = 3.72$, $p = 0.004$). No significant protective effects were found for amlodipine or perindopril. Hyperuricemia is highly prevalent and often unrecognized in the community. Thiazide or loop diuretics and physical height are key contributors to elevated SUA. Community pharmacists are well-positioned to perform opportunistic screening to mitigate cardiometabolic risks associated with elevated uric acid.

Rezumat

Acest studiu transversal a avut ca obiectiv evaluarea prevalenței hiperuricemiei și identificarea factorilor farmacologici și antropometrici care influențează nivelurile de acid uric seric (AUS) în cadrul farmaciei comunitare din România. Datele au fost colectate de la 377 de participanți (cu vârste cuprinse între 18 și 89 de ani) din două farmacii din județul Călărași. Măsurătorile au inclus AUS, tensiunea arterială, glicemia à jeun și IMC. S-a utilizat regresia liniară multivariabilă cu imputare multiplă pentru a identifica factorii predictivi ai nivelurilor de AUS. Prevalența hiperuricemiei a fost de 40,4% în rândul participanților cu niveluri măsurabile. Diureticele cu potență ridicată, indapamida și furosemidul, au fost puternic asociate cu niveluri mai ridicate de AUS ($\beta = 1,22$, $p < 0,001$). Înălțimea s-a evidențiat ca un factor predictiv independent semnificativ ($\beta = 3,72$, $p = 0,004$). Nu s-au constatat efecte protectoare semnificative pentru amlodipină sau perindopril. Hiperuricemia are o prevalență ridicată și este adesea neidentificată în comunitate. Diureticele tiazidice sau de ansă și înălțimea fizică sunt factori importanți care contribuie la creșterea nivelului de acid uric seric.

Keywords: hyperuricemia, uric acid, indapamide, furosemide, community pharmacist, point-of-care testing

Introduction

Hyperuricemia (elevated serum uric acid levels) is increasingly recognized as a major global health concern spanning multiple medical specialties. While classically managed by rheumatologists due to gout, its role as a key contributor to chronic kidney disease, hypertension, cardiovascular events, and metabolic syndrome/diabetes makes it a multifaceted metabolic disorder (1). Its clinical spectrum ranges from asymptomatic elevation through acute gouty arthritis, chronic tophaceous gout, nephrolithiasis, and nephropathy, to emerging associations with cardiovascular disease and metabolic syndrome. The pathophysiology implicates both impaired renal urate excretion and excessive purine catabolism, with the NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasome serving as the central immunological effector in crystal-induced inflammation (2,3).

Hyperuricemia is a condition that is widely prevalent worldwide, especially in high- and middle-income countries (4). The prevalence of hyperuricemia varies significantly across geographic regions, ethnicities, dietary habits, and economic conditions. Recent trends have shown an increasing prevalence of hyperuricemia (5). Reports indicate that the global prevalence rate ranges from 2.6% to 36% across populations (6). Hyperuricemia is substantially more prevalent in men (approximately 20–30%) than in premenopausal women (5–15%), a finding attributed to the uricosuric effects of estrogen, which upregulate ATP-binding cassette sub-family G member 2

(ABCG2)-mediated renal urate excretion. Post-menopausal women approach male prevalence rates (7). Risk conditions for hyperuricemia include well-known dietary, comorbid, and genetic factors. Hyperuricemia is associated with obesity, hypertension, diabetes, dyslipidemia, kidney disease, eating habits, and genetic factors (8–14).

Hyperuricemia can also be a prevalent, mechanistically diverse, and clinically consequential complication of modern pharmacotherapy that remains underrecognized in clinical practice. Diuretics, low-dose aspirin, calcineurin inhibitors, antituberculosis agents, cytotoxic chemotherapy, and antiretroviral drugs can elevate serum uric acid through distinct mechanisms: volume depletion, transporter inhibition, enhanced purine catabolism, or reduced glomerular filtration (15-18). Thus, serum uric acid (SUA) values span a continuum from borderline elevations to clinically significant hyperuricemia (19,20).

Maintaining uric acid levels within the normal physiological range is important, as elevated concentrations can be a risk factor for various metabolic disorders. Research from multiple epidemiological studies highlights that managing hyperuricemia may help mitigate the risk of conditions such as hypertension, metabolic syn-drome, insulin resistance, dyslipidemia, type II diabetes, kidney disease, and cardiovascular events (21,22). By addressing elevated uric acid levels, individuals may improve their overall health and reduce the likelihood of these associated diseases (23–32). Studies have demonstrated that serum uric acid levels can also predict the onset of hypertension, diabetes, obesity, and renal disorders (33-35). It was found that an increased level of uric acid causes a decrease in 25 OH Vitamin D (calcidiol); therefore, hyperuricemia should involve the investigation of its level (36).

Hyperuricemia in Romania has a significant prevalence of approximately 17.6%, being more common in men (30.5%) than in women (17.8%), with a higher incidence in rural communities (37). It is closely associated with metabolic diseases, having a co-occurrence rate of over 81% with dyslipidemia in patients with uncontrolled type 2 diabetes. Key factors include lifestyle, diet, and obesity (37,38). Cardiovascular diseases are the leading cause of death in Romania, with a total number of deaths in 2024 of 130,441, of which essential hypertension accounted for 19,488 deaths, hypertensive heart disease accounted for 13,358 deaths, ischemic heart disease accounted for 25,411 deaths, acute myocardial infarction accounted for 16,142 deaths, stroke not specified as hemorrhagic or as infarction, and cardiomyopathy accounted for 4,483 deaths (39). Diabetes induced a total of 2,869 deaths, while chronic kidney disease (CKD) generated a total of 2,577 deaths (39).

In the URRAH study of diabetic patients, it was found that hyperuricemia was a predictor of overall mortality, but its predictive value was lower when dyslipidemia was included in the statistical analysis. Uric acid levels greater than 5.6 mg/dl among diabetic patients may indicate the presence of metabolic syndrome (40). High uric acid levels are associated with insulin resistance (HOMA index), but genetic analyses have not confirmed this association, and the causal role of uric acid in insulin resistance remains unclear (41) Uric acid levels are also significantly higher among undiagnosed or uncontrolled hypertensive patients compared to those who were normotensive or controlled (42).

Generally, hyperuricemia is poorly controlled therapeutically, for several reasons, including the intensity of therapy, lack of adherence and persistence, and possible adverse reactions to medications (43). Common medications can contribute to increasing uric acid levels, including diuretics with a well-known pro-uricemia effect (44). Guidelines recommend frequent prescription of diuretics in the treatment of hypertension (45). Although diuretics have been associated with elevated uric acid levels, researchers found that antihypertensive therapy was modified in the sense that the diuretic was replaced with another antihypertensive in only 3% of cases when patients were diagnosed with gout (46,47).

Research focusing on community pharmacists actively identifying or screening for undiagnosed hyperuricemia, such as through routine point-of-care uric acid tests in patients without symptoms, is relatively limited in the existing literature. In New Zealand, the Community Pharmacy Gout Management Service (CPGMS) involves pharmacists conducting point-of-care serum urate tests, but it is aimed at patients who have already been diagnosed with gout (48). Laboratory testing in pharmacies is not designed for diagnostic purposes but rather for screening and, if needed, providing medication advice. In Italy, specific administrative decrees (n° 69/2009; n° 153/2009) outline the services that all pharmacies can offer and specify the essential analytical tests to be provided, including those for uric acid (49). Community pharmacists are ideally placed to contribute to public health by delivering such screening services, given their frequent patient contact, accessibility, and established expertise in preventive care and medication review. This role is particularly relevant because even modest elevations in serum uric acid carry significant cardiometabolic consequences; for instance, each 1 mg/dL increase in serum uric acid has been associated with approximately a 13% higher risk of hypertension (50). Therefore, the current study, conducted as a health examination survey on 377 participants aged 18 or older, aimed to assess serum uric acid levels and their association with diagnosis, treatment, and

related parameters, including systolic and diastolic blood pressure, pulse rate, height, weight, and fasting glucose.

Materials and Methods

Study Protocol

The present study is a cross-sectional health examination survey of a convenience sample of the population from Călărași County, approved by the Institutional Ethics Committee of "Carol Davila" University of Medicine and Pharmacy (Approval Number 7462/14.03.2023). The selection method was convenience sampling, based on participants' availability and proximity (51,52). Therefore, the health status of adults who visited 2 community care pharmacies in Calarasi County, Romania, during June - September 2025 was evaluated.

Participants were eligible for inclusion if they were 18 years or older and provided consent for survey participation (completion of a detailed questionnaire), physical measurements (assessment of height, weight, pulse rate, and systolic/diastolic blood pressure) and biochemical analyses (measurement of fasting glucose and serum uric acid (SUA) levels). Patients under 18 years of age and those who did not follow the study protocol were excluded. The questionnaire included questions on baseline data (age, gender), diagnosis (whether a diagnosed health problem was already known), and medication used.

Systolic and diastolic blood pressure and pulse rate were measured with the Microlife BP A2 Classic blood pressure monitor (Microlife Corporation, Widnau, Switzerland), while weight was measured with the Microlife WS 80 Digital Weight scale (Microlife Corporation, Widnau, Switzerland). Fasting glucose and uric acid levels were determined with an Easy Touch GCU device (Contec Medical Systems Co., Ltd., Qinhuangdao, China).

Participants with values above normal limits were referred to medical services for detailed investigations. The selected patients signed the informed consent, and their identification information (name, personal numeric code) was anonymized prior to data analysis.

Variable Definition and Classification

Pharmacological Classification of Medications

To assess the potential pharmacological effects of medications on serum uric acid levels, we developed four binary indicators based on the known mechanistic effects of the medicinal products in the dataset on urate metabolism. Firstly, medications that significantly increase uric acid, such as loop or thiazide-like diuretics (furosemide, indapamide), were identified due to their well-established role in reducing renal urate excretion. Secondly, a moderate-risk category included drugs that raise uric acid through metabolic or renal pathways: low-dose acetylsalicylic acid, olanzapine, risperidone, and spironolactone. Thirdly, a weak-risk category encompassed medications with minor or theoretical urate-raising effects, including β-blockers (bisoprolol, metoprolol, nebivolol, carvedilol), candesartan, phenobarbital, carbamazepine, and valproic acid. Fourthly, a urate-lowering category identified drugs with protective effects on serum uric acid: allopurinol (xanthine oxidase inhibition), SGLT2 inhibitors (dapagliflozin, empagliflozin), fenofibrate (uricosuric effect), alpha-lipoic acid (mild urate-lowering activity), amlodipine, and losartan. A fifth binary indicator flagged patients for whom all substance fields contained only the placeholder value "0", indicating no active pharmacological treatment. Each indicator was created by pattern-matching across the entire list of medications using case-insensitive regular expressions. To identify patients exposed to both urate-lowering and urate-raising agents simultaneously, we devised a mixed-effect variable coded as 1 when at least one urate-lowering medication and at least one urate-increasing medication (strong, moderate, or weak) were present in the same record. Using these indicators, we developed an ordinal classification variable according to a hierarchical rule: mixed-effect exposure; urate-lowering medications only; strong urate-raising medications; moderate-risk medications; weak-risk medications; and no known uric-acid-modifying drugs.

Due to the frequent occurrence of polypharmacy, where patients received medications from opposing pharmacological classes, a conflict-resolution rule was implemented before final classification. A patient was categorized as Mixed only if at least one uric acid-lowering substance and one uric acid-raising substance (from any of the three raising-effect tiers) were present simultaneously. This category thus captures genuine pharmacological antagonism within the same regimen, where the net effect on serum uric acid cannot be determined solely by medication class. For all remaining patients (those not exhibiting simultaneous raising and lowering exposure), a strict descending priority rule was applied, assigning each patient to the highest applicable category (Table I).

The resulting variable was categorized as an ordered factor with seven levels (0-6), representing a predetermined clinical gradient ranging from no pharmacological exposure to progressively stronger uric acid-modifying effects. The Mixed category was placed at the top to indicate irreducible pharmacological uncertainty rather than a definitive increase or decrease effect.

Table I

Descending priority rule was applied, assigning each patient to the highest applicable category

Ordinal level	Label	Assignment rule
6	Mixed effects	Uric acid-lowering substances present alongside at least one raising-class substance
5	Lowers uric acid	Uric acid-lowering substances present, no raising-class substances
4	Strong diuretics	Strong uricosuric diuretic present, no lowering substances
3	Moderate evidence	Moderate uric acid-raising substance present, no diuretics or lowering substances
2	Weaker evidence	Weaker or inconsistent uric acid-raising substance present only
1	Neutral	Medications present, but none matching any pharmacologically flagged substance
0	None	No medications recorded

The "neutral" category included a wide range of medications: apixaban and rivaroxaban; moxonidine, perindopril, ramipril, captopril, enalapril, amiodarone, trimetazidine, and nicergoline; levothyroxine; metformin (including variants), gliclazide, sitagliptin, semaglutide, and insulin; rosuvastatin, atorvastatin, and ezetimibe; alendronic acid, risedronic acid; colecalciferol, ferrous (iron) supplements, magnesium, potassium aspartate, and magnesium aspartate; tramadol, etoricoxib, paracetamol, piroxicam, prednisone, methylprednisolone, budesonide, formoterol, tiotropium/olodaterol, tamsulosin, dutasteride, *Serenoa repens*, trospium, betahistine, paroxetine, trazodone, lorazepam, clopidogrel, omeprazole, diosmin, codeine, guaiacosulfonate, silibinum, pentaerythrityl, desloratadine. Here we also included food supplements declared as used by the patients.

Diagnostic Cluster Classification

Comorbidity burden was characterised by grouping each patient's free-text diagnostic field into one of ten mutually exclusive clinical categories using a hierarchical keyword-matching algorithm applied to the raw Romanian-language diagnostic entries. Classification was performed using case-insensitive regular expression matching, which inherently accommodated variation in capitalisation, and was applied sequentially such that each patient was assigned to the first matching category in the priority order described below. Diagnoses had been recorded as unstructured free text in Romanian, and entries exhibited considerable heterogeneity including standard abbreviations (e.g., *HTA* for hypertension, *IMA* for myocardial infarction, *ICC* for congestive heart failure), partial phrases (e.g., *ins. renal* as a truncation of *insuficiență renală*), and common spelling variants or typographic inconsistencies. These were addressed by matching on root substrings rather than complete terms wherever possible (e.g., *dislipidemi-* captures both *dislipidemie* and *dislipidemii*), and by including all attested abbreviations and partial forms explicitly in the keyword list. Entries explicitly recorded as unspecified (e.g., *fără diagnostic*, *nu a precizat*, *psihiatrie nu a precizat*) and missing values were assigned to a dedicated None category.

The hierarchical classification proceeded in the following fixed order, with higher-priority categories taking precedence over all lower ones: (1) Gout / Hyperuricemia: highest priority, given direct aetiological relevance to the outcome variable; overrides all other categories; (2) Renal : given the dominant role of renal clearance in uric acid homeostasis; (3) Metabolic/Cardiometabolic: hypertension, dyslipidaemia, diabetes, hepatic steatosis; explicitly excludes entries also matching gout or hyperuricemia keywords; (4) Cardiovascular: structural and arrhythmic cardiac disease not captured above; (5) Thyroid/Autoimmune: thyroid disorders and systemic autoimmune conditions; (6) Musculoskeletal: osteoporosis, spondylosis, disc pathology, non-gout arthropathy; (7) Psychiatric/Neurological: psychiatric diagnoses and neurological conditions including stroke; (8) Respiratory: chronic obstructive pulmonary disease, asthma, pneumonia; (9) Gastrointestinal/Other: gastrointestinal pathology, neoplasia, anaemia, menopause, prostatic disease; (10) None: no diagnosis recorded or entry explicitly unspecified; (11) Other/Unclassified: residual category for entries not matching any keyword.

Statistical Analysis

To address missing data, multiple imputation by chained equations (MICE) was used, as implemented in the R “mice” package. A total of 50 imputed datasets were created using predictive mean matching (PMM) with 100 iterations to ensure convergence and a fixed random seed (123) to maintain reproducibility. PMM was chosen because it preserves the distributional properties of continuous variables without requiring normality assumptions.

Continuous variables were summarised as mean ± standard deviation (SD) when approximately normally distributed, and as median with interquartile range (IQR) when the distribution was markedly skewed or when visual inspection of histograms and formal testing suggested meaningful departure from normality. Categorical variables were summarised as absolute frequencies and percentages.

For each imputation, descriptive statistics for serum uric acid levels were calculated by group, including sample size, mean, variance, standard deviation, median, and interquartile range (IQR). These statistics were computed separately for each category across all ten imputed datasets (None, Weaker evidence, Moderate evidence, Strong evidence/diuretics,

Lowering uric acid, and Mixed effects medicinal products). Mean point estimates were pooled across imputations using Rubin's rules, combining within-imputation and between-imputation variances to obtain a total pooled variance, with 95% confidence intervals derived using a t-distribution and degrees of freedom estimated by Barnard and Rubin's (1999) method (53). For the median and interquartile range, where no closed-form pooling rules exist, point estimates were averaged across the ten imputed datasets, and 95% confidence intervals were constructed using a percentile bootstrap approach with 2,000 resamples from the imputation-specific estimates.

To distinguish the potential hyperuricemic impact of indapamide from the effects of other drugs that influence uric acid metabolism, a restricted comparison dataset was created from each imputed dataset. The analysis focused on two distinct groups: those using indapamide (n = 66) and individuals not taking any medications that affect uric acid (n = 233 in the imputed dataset). This excluded patients on drugs with uric acid-lowering, uric acid-raising, or mixed effects. This approach aimed to provide a clearer comparison between the group exposed to indapamide and a reference group not influenced by other pharmacological factors that affect uric acid levels. Descriptive statistics for serum uric acid were calculated for each group across all ten imputed datasets and combined using the same approach as before - Rubin's rules for the mean with 95% confidence intervals derived from a t-distribution with Barnard-Rubin degrees of freedom, and a percentile bootstrap (2,000 resamples) for the median and interquartile range.

To assess the robustness of our findings, we complemented the multiple imputation analysis with a sensitivity analysis of the original observations. This 'non-imputed' dataset was restricted to participants with non-missing uric acid data.

Previous reports suggested that amlodipine and perindopril might protect against increases in plasma uric acid levels (54,55) therefore, we explored this effect in our dataset. However, among the 70 patients taking indapamide or furosemide, only 16 were also taking amlodipine, and 40 were taking perindopril. To investigate this potential effect, we conducted an independent-samples t-test (Welch) on complete cases, yielding 60 observations after excluding 11 cases with missing plasma uric acid data. This version of the t-test was chosen over Student's t-test because it does not require the assumption of equal variances between groups, making it more suitable for situations where group sizes or variances might vary. Given the exploratory nature of our analyses and the relatively small amount of missing data (15.71%), we did not employ multiple imputation. The comparison groups were defined as follows: patients who received a diuretic (either furosemide or indapamide) along with the antihypertensive agent of interest (amlodipine or perindopril, respectively) were compared to patients who received the same diuretic without the additional prescription. Each comparison was thus conducted within the subset of patients using diuretics, isolating the incremental association of the co-prescribed agent.

This sub-analysis was limited to complete cases, focusing only on patients who had no missing data for any of the variables involved in the comparison. MICE imputation was not utilized here for two main reasons. The first is that the sub-analysis aims to be descriptive and hypothesis generating; the added inferential complexity from imputation would not align with this exploratory goal. Secondly, the subgroups defined are small, and applying imputation models within such narrow groups increases the risk of model misspecification and unstable imputed values.

Multivariable Regression Model

To determine the factors influencing serum uric acid levels, a multivariable linear regression model was utilized, integrating field knowledge with information-theoretic model selection and multiple imputation. SUA served as the primary outcome variable, measured as a continuous value (mg/dL). Initially, a comprehensive model was defined in advance, including a list of 13 potential predictors: (1) sex, (2) age, (3) systolic blood pressure, (4) diastolic blood pressure, (5) fasting glucose, (6) pulse rate, (7) BMI, (8) height, (9) weight, (10) diagnostic cluster, (11) category of uric acid-related medication, (12) number of active pharmaceutical substances, and (13) duration of medication use. This global model was applied separately to each of the ten imputed datasets. The model selection procedure involved an exhaustive search using the dredge function from the MuMIn R package (2), with the corrected Akaike Information Criterion (AICc) as the ranking metric. Model subsets were limited to include between one and thirteen predictors. Candidate model subsets were restricted to a minimum of one and a maximum of 13 predictors. The importance of each variable was measured by calculating variable importance weights, computed by summing Akaike weights (sw()) across all models within each imputed dataset's model set; these importance scores were then averaged across the ten imputations. This method identifies variables that consistently enhance model fit across the entire model space, regardless of the specific model chosen.

To develop a final model that could be pooled across multiple imputations, the top-ranked model (with the lowest AICc) from each imputed dataset was selected. Before counting frequencies, variables were reduced to their fundamental terms (i.e., individual levels of categorical predictors that were dummy-coded were linked to their main variable). A variable

was included in the consensus model if it appeared in the best model of at least half of the imputed datasets (i.e., 25 or more out of 50 imputations), aligning with guidelines for variable selection in multiple imputation contexts. Using this criterion, the consensus model driven by data retained two predictors: height and the number of active substances (medicinal products). However, since the pharmacological category of medications affecting uric acid directly relates to serum uric acid metabolism, it was deemed a more clinically informative replacement for the count of active substances (field knowledge directly relevant for selection). To empirically test this replacement, an alternative model substituting the number of active substances with uric acid-influencing medications was applied to all ten imputed datasets. The pooled adjusted R^2 of this alternative model was slightly higher than that of the data-driven consensus model, offering quantitative evidence for the substitution. A similar approach of replacing height with other anthropometric measures did not improve the pooled adjusted R^2 (whereas height, as discussed below, has some independent validation in a previous study). Consequently, the final model included height and the category of uric acid-related medications as predictors. This model was applied to each of the 50 imputed datasets within the mice framework, and regression coefficients were combined using Rubin's rules through the pool() function. Pooled estimates are reported with 95% confidence intervals and two-tailed p-values.

The overall explanatory power performance of the final model was evaluated by examining both the pooled R^2 and the adjusted R^2. Additionally, the fraction of missing information (FMI) for each pooled estimate was reported to indicate the extent to which missing data contributed to the parameter uncertainty.

To verify the assumptions of linear regression, diagnostic checks were conducted on a single representative imputed dataset. Residual plots, which compare residuals to fitted values, were examined to assess the linearity between predictors and the outcome and to detect any systematic patterns in the residuals. Homoscedasticity of residuals was visually evaluated using a scale-location plot and formally tested with the Breusch-Pagan test. The normality of residuals was checked by visually inspecting the Q-Q plot, as formal tests often indicate violations even when they are minor. Multicollinearity among predictors was evaluated using the variance inflation factor (VIF), with values under 5 deemed acceptable. Although minor deviations from normality were observed in the residual distribution, they were considered acceptable given the robustness of linear regression to slight departures from normality in samples of this size. No signs of heteroscedasticity or problematic multicollinearity were found. Overall, the diagnostic assessment confirmed that the linear regression model was suitable for the data.

All statistical tests were two-tailed and a significance threshold of $\alpha = 0.05$ was applied throughout. Results with $p < 0.05$ were considered statistically significant; no correction for multiple comparisons was applied given the exploratory nature of the analysis.

All analyses were conducted in R version 4.5.2. The following packages were used: data manipulation and variable derivation were performed with *dplyr* (v1.2.1) (56-58)and *stringr* (v1.6.0); missing data were handled using multiple imputation by chained equations as implemented in *mice* (v3.19.0)(59); multi-model inference and information-theoretic model selection were performed with *MuMIn* (v1.48.19)(60-62). Data were imported from Excel format using *rio* (v1.3.0)(63). All package versions refer to those current at the time of analysis.

Results and Discussion

The study included 377 participants, aged 18 to 89 years, with an average of 56.95 and an interquartile range of 48 to 69. The cohort consisted of 55.17% women and 44.83% men. Among the patients, 183 had not previously taken any medication, while the remaining 184 regularly used 1-9 different medicinal products. A histogram illustrating the distribution of the number of medicinal products used by each patient is shown in Figure 1.

Among the 377 participants, 46.7% (n = 176) identified as healthy volunteers with no recorded chronic diagnoses. Among those with known medical conditions, the largest subgroup was those with cardiometabolic and metabolic diseases, making up 40.1% (n = 151) of the entire cohort and nearly 75% of all diagnosed patients. Other medical conditions were much less common: musculoskeletal and gastrointestinal (GI) disorders each accounted for about 2.1% (n = 8 per category); neurological/psychiatric and cardiovascular-specific conditions were present in 1.9% (n = 7) and 1.6% (n = 6) of participants, respectively. Gout, or known hyperuricemia, was diagnosed in only 1.6% (n = 6) of the group, while thyroid/autoimmune (n = 5), respiratory (n = 4), and renal (n = 2) conditions were underrepresented.

The cohort used a variety of medicinal products, the most frequent of which are shown in Figure 2.

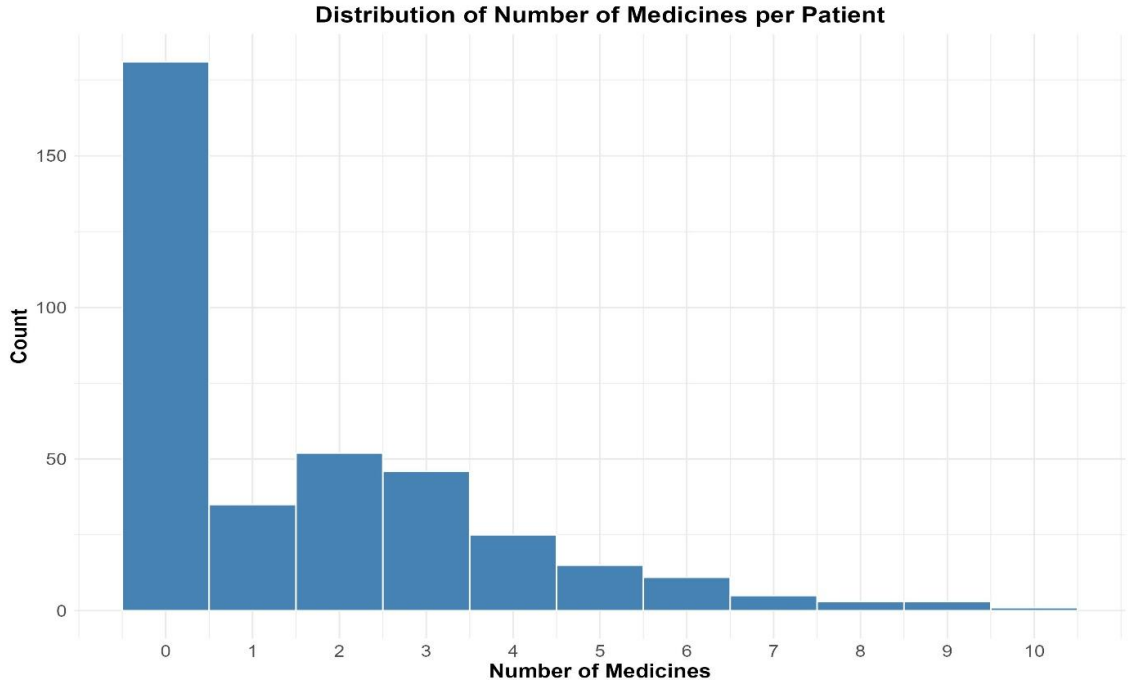

Figure 1.
Distribution of the number of medications per patient across the study population

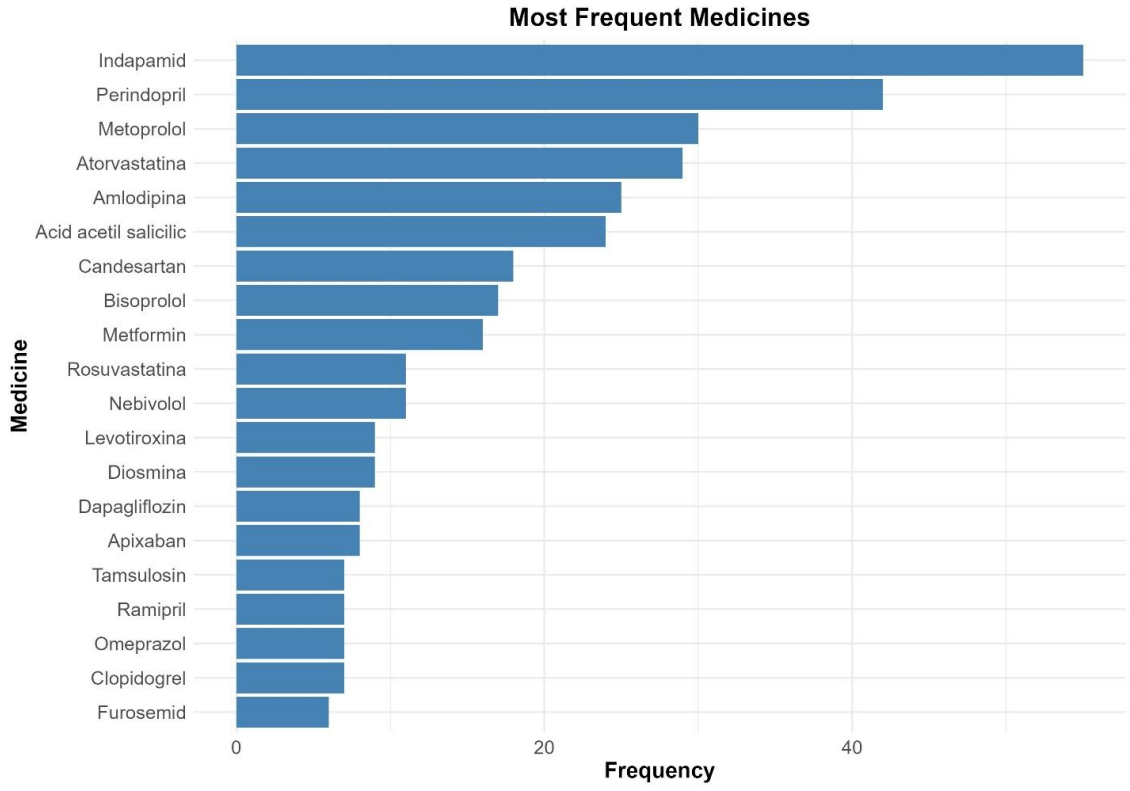

Figure 2.
Distribution of the 20 most frequently prescribed medicines across the study population. Only the top 20 most frequent medicines are shown.

In the study group in which uric acid levels were measurable (N = 252), about 40.4% of patients assessed in the pharmacy setting exhibited hyperuricemia. Within the entire sample, the largest subgroup consisted of patients who were not on indapamide and did not have hyperuricemia, making up 50.8%. Although indapamide users comprised a smaller segment of the overall group (17.5%), the occurrence of

hyperuricemia among them was almost evenly split: 8.8% of the subgroup had indapamide without hyperuricemia, while 8.7% had elevated uric acid levels. Conversely, among those not using indapamide, the percentage of patients with hyperuricemia (31.7%) was significantly lower than that of those with normal uric acid levels (50.8%). Thus, in the indapamide group, the distribution is nearly equal (8.8 vs 8.7), whereas in the non-indapamide group, the ratio of normal to high uric acid levels is approximately 1.6:1 (50.8 vs 31.7). The findings from the non-imputed data were similar, though they indicated a slightly higher prevalence of hyperuricemia among indapamide users (11.5% vs 8.7%) compared to the imputed data. Both analyses reinforce the established clinical link between thiazide-like diuretics and increased serum uric acid. However, as discussed below, the non-indapamide user group was diverse rather than homogeneous, as our further analysis makes clear.

Among patients taking no medicinal products, the proportion with hyperuricemia was 43.4% (95% CI 31.8-55.0%).

Uric acid levels were assessed across seven pharmacological subgroups, each defined by the anticipated impact of patients' medications on uric acid metabolism. The largest group comprised patients not taking any medication (n = 181), with an average uric acid level of 6.00 mg/dL (95% CI: 5.66-6.34) and a median of 6.14 mg/dL (95% CI: 6.06-6.22). Patients on medications with no known influence on uric acid (neutral group, n = 52) exhibited slightly elevated levels (mean 6.41, median 6.31 mg/dL), as did those on medications with weaker evidence of influencing the serum uric acid levels (n = 34; mean 6.37, median 6.28 mg/dL). Those on medications with moderate uricemic impact evidence (n = 18) had a mean of 6.00 mg/dL (95% CI: 5.06-6.94), though the wide confidence interval reflects the small sample size for this subgroup. The highest uric acid levels were found in patients taking strong diuretics, primarily indapamide and to a lesser extent furosemide (n = 51; mean 7.20, 95% CI: 6.50-7.91; median 6.84 mg/dL), and in the uric acid-lowering group (n = 7; median 7.00 mg/dL, IQR: 6.73-8.50), although the latter group was too small to compute reliable mean confidence intervals. Patients on medications with mixed pharmacological effects (n = 34) had intermediate levels (mean 6.80, median 6.54 mg/dL) (Table II). Overall, there was a noticeable trend of increasing uric acid levels with a higher uricemic medication burden, the strong diuretics group showing the most significant increase compared to the no-medication reference group (Figure 3). In general, patients on strong diuretics had consistently higher uric acid levels than those in other groups. The results from the non-imputed data set are presented in Table III.

Table II

Uric acid levels of the patients in the imputed data set, by their use of medicines

Group	n	Mean (95% CI)	Median (95% CI)	IQR
None	181	6.00 (5.66 - 6.34)	6.14 (6.06 - 6.22)	4.72 - 7.17
Neutral	52	6.41 (5.91 - 6.91)	6.31 (6.28 - 6.34)	5.55 - 7.12
Low Risk ↑	34	6.37 (5.66 - 7.09)	6.28 (6.25 - 6.32)	5.18 - 7.15
Mod. Risk ↑	18	6.00 (5.06 - 6.94)	5.90 (5.82 - 5.98)	5.25 - 6.60
High Risk ↑ (Thiazide Diuretics)	51	7.20 (6.50 - 7.91)	6.84 (6.82 - 6.87)	5.49 - 8.37
Urate-Lowering	7	7.50 (NaN - NaN)	7.00 (7.00 - 7.00)	6.73 - 8.50
Mixed effects (lowering + increasing)	34	6.80 (6.13 - 7.48)	6.54 (6.49 - 6.59)	5.73 - 8.00

Table III

Uric acid levels of the patients in the non-imputed data set, by their use of medicines

UricAcid_Meds	n	Mean	SD	Median
None	98	5.79	1.61	5.55
Neutral	39	6.49	1.47	6.30
Weaker evidence	25	6.52	1.96	6.40
Moderate evidence	13	6.10	1.71	6.10
Strong diuretics	42	7.29	2.49	6.95
Lowers uric acid	7	7.50	2.01	7.00
Mixed effects (lowering + increasing)	28	6.85	1.70	6.54

A logistic regression model predicting hyperuricemia as a binary outcome was subsequently explored; however, none of the candidate predictors reached statistical significance after pooling across imputed datasets. This outcome likely highlights the loss of quantitative detail that occurs when a continuous outcome is dichotomized at a diagnostic threshold, further complicated by the small number of hyperuricemia cases available for analysis. Consequently, the continuous model is considered the primary analytical result of this study. Serum uric acid levels were also compared between individuals using indapamide (n = 66) and those not using it (n = 311). The mean serum uric acid level was significantly higher

in indapamide users, averaging 7.01 ± 2.14 mg/dL, compared to 6.21 ± 1.70 mg/dL in non-users (results aggregated from 50 imputations). A similar difference was also evident in the median values, where indapamide users had a median uric acid level of 6.79 mg/dL (Q1-Q3: 5.43 - 7.98), while non-users had a median of 6.27 mg/dL (95% CI: 4.94 - 7.20). These results align with the known hyperuricemic effect of indapamide, a diuretic similar to thiazides. However, the comparison is less relevant because the non-indapamide medications are more diverse (as discussed above, they were categorized into six groups). The data for the subset without imputation is presented in Table IV.

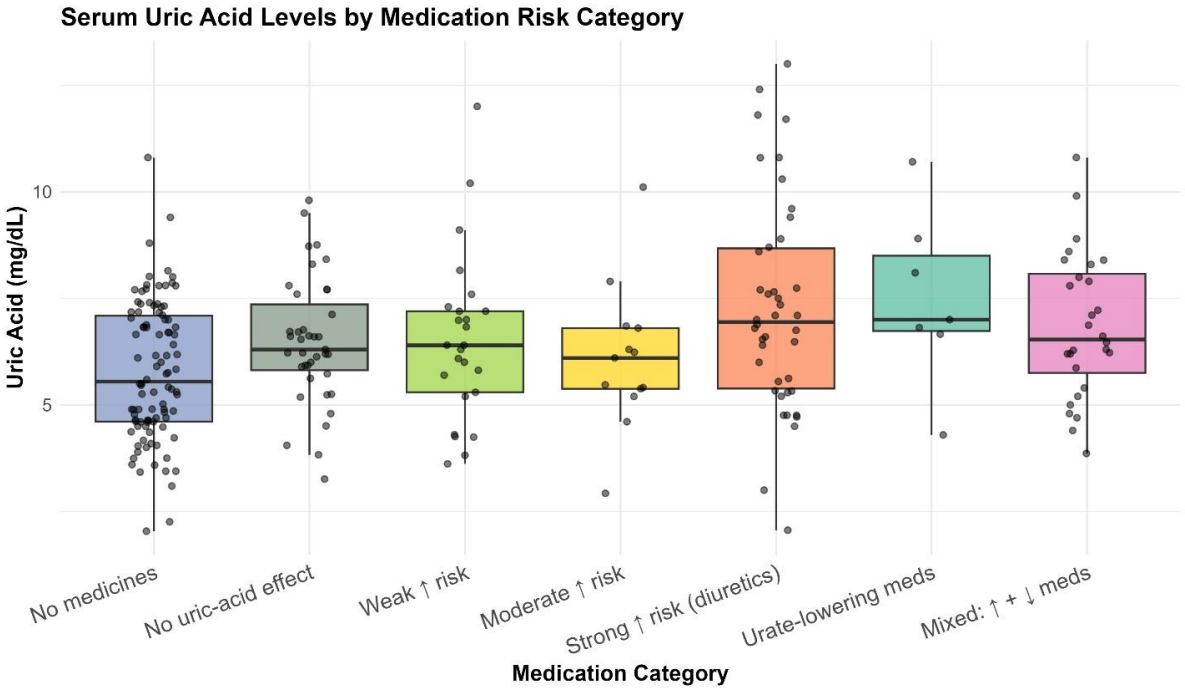

Figure 3.

Distribution of serum uric acid levels across medication risk categories. Boxplots show the median and interquartile range (IQR); individual data points are jittered to show data density. Medication categories are defined based on their known clinical impact on urate levels, ranging from urate-lowering therapies to high-risk diuretics

Table IV

Comparison among the uric acid levels in patients using indapamide and non-users of indapamide based on the non-imputed data set

Indapamide_fct	n	Mean	SD	Median	Q1	Q3	Min	Max
Non-users	197	6.2	1.8	6.2	4.9	7.2	2.0	12
Indapamid users	55	7.1	2.2	6.9	5.4	8.2	2.1	13

The final multivariable linear regression model, fitted across 50 datasets with multiple imputations and pooled using Rubin's rules, identified two predictors for serum uric acid levels: height and the category of uric acid-related medication. The model accounted for 8.5% of the variation in serum uric acid (pooled adjusted $R^2 = 0.085$, 95% CI: 0.027-0.168). The fraction of missing information (FMI) for the entire model was 0.44, suggesting that a significant portion of the uncertainty in the estimates is due to missing data.

Height, expressed in metres, was independently associated with higher serum uric acid levels ($\beta = 3.72$, 95% CI: 1.18-6.26, $p = 0.004$). This relationship was consistently observed across all 50 imputed datasets, making it the most reliably selected predictor in the model, as it was included in the best-fitting model for all 50 imputations.

Regarding the medication category, the reference group consisted of patients not on any medication affecting uric acid levels. Compared with this group, those taking potent diuretics exhibited notably higher serum uric acid levels ($\beta = 1.22$, 95% CI: 0.56-1.88, $p < 0.001$). Patients on medications with a mixed impact on uric acid, involving both lowering and increasing mechanisms, also had significantly elevated levels relative to the reference group ($\beta = 0.87$, 95% CI: 0.11-1.64, $p = 0.026$). Likewise, individuals on medications intended to lower uric acid showed higher serum uric acid levels than those in the reference group ($\beta = 1.47$, 95% CI: 0.14-2.80, $p = 0.031$). However, this result should be inter-preted with caution due to the wider confidence interval and

the clinical complexity of this category, which may reflect an indication bias in which patients prescribed uric acid-lowering drugs already had high baseline levels.

The remaining medication categories - neutral (β = 0.35, 95% CI: −0.32-1.02, p = 0.308), weaker evidence (β = 0.34, 95% CI: −0.41-1.08, p = 0.373), and moderate evidence (β = −0.01, 95% CI: −0.98-0.95, p = 0.978), did not differ significantly from the reference group.

The consistency of results across analyses with 30 and 50 imputations, with point estimates varying by no more than 0.05 for all terms, indicates that the imputation process has adequately converged. Collectively, these results imply that both height and the use of medications known to raise uric acid levels, especially potent diuretics and drugs with mixed mechanisms, are independently linked to serum uric acid levels in this sample. However, the modest explained variance and substantial missing data suggest that a large portion of the variability in uric acid levels is not accounted for by the predictors in our dataset.

Indapamide was used by 55 patients (13.9% of the sample), but the distribution across dose levels was notably uneven. Most patients were prescribed 1.5 mg (n = 32), while only a few received other doses: 0.625 mg (n = 6), 1.25 mg (n = 10), and 2.5 mg (n = 4). This uneven distribution prevented a reliable dose-response analysis. Consequently, the potential impact of indapamide dosage on serum uric acid levels remains an unresolved issue that could not be explored with the current data.

Best on Welch two-sample t-tests, there were no statistically significant differences in uric acid levels between patients treated with amlodipine (p = 0.693) or perindopril (p = 0.425) and those who were not treated with these medicinal products. Although both treatment groups showed numerically lower average concentrations of uric acid (7.01 *vs*. 7.22 mg/dL for amlodipine and 6.95 *vs*. 7.43 mg/dL for perindopril), suggesting a potential protective effect, the 95% confidence intervals for the mean differences (−0.86 to 1.28 and -0.72 to 1.69, respectively) encompassed zero. Therefore, given the wide confidence intervals and relatively small sample sizes, these analyses may lack sufficient statistical power to detect small but clinically relevant effects.

Our findings indicate that among patients with measurable uric acid levels (N = 252), approximately 40.4% evaluated in the pharmacy setting showed signs of hyperuricemia. Notably, even among those not using any medications, 43.4% (95% CI 31.8-55.0%) had hyperuricemia. This percentage is higher than the typical rates reported in global adult populations, though not excessively so. Worldwide prevalence rates have been documented to range from 2.6% to 36% across different populations, with Finland reporting a rate of 48%, broken down by gender to 60% in males and 31% in female (64). In Romania, a previous study carried out among the rural Romanian population reported 17.6% prevalence, but in that study, there was an obvious sex imbalance (only 29.6% of the sample were males, but in males, hyperuricemia had a 30.5% frequency as compared with 17.8% for females)(65). This higher value may reflect selection bias, as the study group was drawn from a relatively small area in Southern Romania.

Among the 377 participants, 46.7% (n = 176) were identified as healthy volunteers without any chronic diagnoses on record. However, it is plausible that a significant number of these individuals might have undiagnosed conditions such as cardiovascular diseases or diabetes. For example, the PREDATOR national study revealed that 47.38% of the Romanian adult population had hypertension, with many cases either undiagnosed or inadequately managed.(66) Similarly, a 2021 study utilizing mobile health caravans in rural Romania reported a notably high hypertension prevalence of 72.8% among screened adults, with 33.3% being newly diagnosed (previously undiagnosed before the screening)(67). Consequently, it is probable that cardiovascular diseases and other health issues affect the seemingly healthy participants in our study, which might also account for the elevated incidence of hyperuricemia.

The discovery of a significant number of cases of hyperuricemia, many of which appear to be previously unrecognized or untreated, highlights the potential of community pharmacies as effective sites for opportunistic screening. Hyperuricemia often presents without symptoms, leading many individuals to delay seeking medical care until complications develop. In Romania, rural regions face substantial obstacles to preventive healthcare, including a shortage of physicians, geographic remoteness, and a tendency toward lower healthcare-seeking behavior. By providing point-of-care uric acid (and similar) testing, pharmacists can serve as an initial public health checkpoint, facilitating early detection, risk assessment, lifestyle guidance, and prompt referrals to doctors before conditions progress to gout, hypertension, chronic kidney disease, or cardiovascular issues.

The variation in serum uric acid levels observed among the seven pharmacological subgroups supports the hypothesis that different medications have distinct effects on uric acid levels, as evidenced by both univariate and multivariate analyses. Patients not on uricemic drugs had the lowest average uric acid level (6.00 mg/dL), which is closely aligned with population-based reference values (68). In the United States, epidemiological research has typically recognized 7.0 mg/dL as the maximum threshold for adult males and 6.0 mg/dL for females, with hyperuricemia being defined at 7.0 mg/dL (69);

therefore, an average of 6.00 mg/dL in a drug-naïve group of both sexes falls within the reference norms based on population data. Conv-ersely, in our data set, those on potent diuretics, mainly indapamide and furosemide, exhibited the highest average level (7.20 mg/dL), a clinically significant increase that underscores the well-established hyperuricemia potential of loop and thiazide-like diuretics.(70) There is well-established evidence that thiazide and loop diuretics, including indapamide and furosemide, reduce renal urate excretion by increasing proximal tubular reabso-rption. As described by Feig et al., diuretic-induced volume contraction enhances urate reabsorption, contributing to hyperuricemia (71). Furthermore, a large population-based study by Choi HK et al. confirmed that diuretic use is an independent risk factor for incident gout, with a dose-dependent relationship between exposure and serum urate levels (72).

In contrast, patients who either did not receive medication or were treated with drugs deemed neutral or only weakly linked to urate metabolism showed similar or lower uric acid levels. This observation supports the idea that, in the absence of strong pharmacological effects, serum urate levels are primarily influenced by renal processing and metabolic factors. Rather curiously, the group receiving uric acid-lowering treatment (n = 7) show-ed a median level of 7.00 mg/dL, surpassing that of the no-medication group. Although this might initially seem contradictory, it likely indicates that these patients were prescribed urate-lowering therapy due to pre-existing hyperuricemia or gout, rather than suggesting treatment failure. This may also indicate confounding by indication, poor adherence, or inadequate dose adjustment, as obs-erved in real-world studies on gout management (73)

Groups with neutral or weaker evidence of effects on uric acid showed only slight increases relative to the no-medication reference, indicating that not all pharmacological effects are clinically significant. However, the cross-sectional nature of the study limits the ability to draw causal conclusions, and the possibility of residual confounding due to underlying conditions (such as hypertension or chronic kidney disease) cannot be ruled out. Future prospective research should focus on standardizing medication exposures, incorporating repeated uric acid measurements, and exploring whether adjusting uricemia medications strongly (when clinically possible) can lower serum urate levels and reduce related cardiovascular or renal risks.

The lack of statistically significant differences across the remaining medication categories should be interpreted with caution, given the confidence intervals and the study's statistical power. Non-significant results do not imply equivalence with the reference group; rather, they suggest that the data are consistent with both the presence and absence of a clinically meaningful association (74). This distinction is important because studies with limited accuracy or moderate variability may fail to detect true effects, even when point estimates suggest their presence. Additionally, non-significant regression coefficients can arise from several factors, such as inadequate statistical power, measurement variability, or shared variance with other covariates in the model, particularly in multivariable settings. As a result, the current findings suggest that these medication categories do not exhibit a clear link with uric acid levels in this sample. However, they do not rule out the possibility of significant effects, thereby justifying further research in larger or more precisely measured cohorts.

The final multivariable linear regression model, which included height and uric acid-related medication category as significant predictors, explained only 8.5% of the variability in serum uric acid levels, although we also included as potential independent variables sex, age, blood pressure, fasting glucose, pulse rate, BMI, weight, diagnostic cluster, number of active pharmaceuticals, and medication duration. This modest explanatory power (which is common in multivariate clinical outcomes) likely stems from the exclusion of key unmeasured or unavailable factors that strongly influence uric acid homeostasis, such as dietary intake (e.g., purine-rich foods like red meat or seafood, fructose consumption, and alcohol)(75), genetic predispositions (e.g., variants in SLC2A9 or ABCG2 genes), renal function markers (e.g., eGFR or fractional urate excretion)(76), and comorbidities like chronic kidney disease.(77)

Our findings are consistent with previous research showing a positive association between height and the risk of hyperuricemia, especially in non-overweight populations. For example, Shimizu et al. (2013) found that taller Japanese men, particularly those with a BMI < 25 kg/m², faced a higher risk of hyperuricemia. They hypothesized that early-life social and physical conditions, such as nutrition and growth patterns, might predispose individuals to metabolic issues in adulthood (78). This suggests that height, as an indicator of developmental exposures, could represent the cumulative biological and environmental influences on UA metabolism. Further supporting this connection, Sato et al. (2015), from the same research group, identified body height, along with drinking status and serum creatinine, as a key factor in the relationship between hyperuricemia and carotid atherosclerosis in Japanese men (79). This indicates that height may not only directly affect SUA levels but also interact with vascular risk factors, possibly through shared pathways involving oxidative stress or endothelial dysfunction. Additionally, Yoon et al. (2022) reported that growth hormone (GH) therapy in children with

idiopathic short stature increased SUA levels, reinforcing the biological plausibility of a height-UA relationship. The authors considered elevated SUA levels a favorable marker of GH responsiveness, though they cautioned that its long-term clinical significance, particularly regarding hyperuricemia, warrants further investigation (80)

The exclusion of sex from our consensus model is worth discussing, given its well-documented role as a predictor of serum uric acid. Although sex was considered as a candidate variable and achieved a variable importance score of 0.358 (indicating its presence in a significant portion of the model ensemble) it was not included in the selected final model. The most straightforward explanation for this is the collinear relationship between sex and height. Height emerged as the strongest predictor in the full candidate set (variable importance = 0.921) and is well-known to sexually dimorphic, with men generally being taller than women. Since the sex difference in serum uric acid is partially mediated by lean body mass and body composition, both of which correlate with height, it is statistically expected that height would absorb a substantial proportion of the sex-contributing variance in SUA when both variables compete within the same model selection process. In this selection, a predictor whose marginal contribution is minor compared to a correlated, more significant variable, will be left aside; in other words, sex is statistically redundant rather than biologically irrelevant. This interpretation is consistent with the literature, which shows that anthropometric variables can serve as proxies for physiological differences related to sex in metabolic outcomes. An importance score of 0.358 for sex indicates genuine but non-independent explanatory value, and should not be seen as a lack of biological signal.

We found no statistically significant differences in SUA levels between patients treated with amlodipine ($p = 0.693$) or perindopril ($p = 0.425$) and those not receiving these medications. These find-ings are consistent with some prior studies. For instance, a study indicated that amlodipine did not significantly impact serum uric acid levels in individuals with hypertension, reinforcing the idea that calcium channel blockers like amlodipine may not consistently reduce uric acid levels across all groups (81). Conversely, other studies have shown that amlodipine can lower uric acid levels in certain situations. Chanard et al. (2003) found that amlodipine significantly reduced serum uric acid levels in hypertensive patients who had undergone renal transplantation, suggesting that its uricosuric effects might be more evident in patients with renal dysfunction or those taking cyclosporine, which is known to cause hyperuricemia (55). Additionally, a systematic review and network meta-analysis identified the combination of losartan and amlodipine as one of the most effective treatments for reducing uric acid levels in hypertensive patients with hyperuricemia, whereas no such effect was observed with amlodipine alone (82) The findings for perindopril are consistent with a recent study that observed a slight, statistically insignificant decrease in uric acid levels (average reduction: 0.2 mg/dL, $p = 0.08$) among patients with type 2 diabetes mellitus (83) This further corroborates the limited influence of ACE inhibitors like perindopril on uric acid metabolism. Moreover, it is well-established that ACE inhibitors as a group typically exert minimal effects on uric acid levels ("taken together, the evidence does not currently support a clinically meaningful urate-modulating effect by ACE-Is") (84), in contrast to diuretics, which are known to enhance uric acid reabsorption and increase serum levels.

The broad confidence intervals and relatively small sample sizes in our study imply that the analyses might not have had sufficient statistical power to detect small yet clinically significant effects. This limitation is common in clinical research, where wide confidence intervals can mask true differences, especially when the effect size is modest. To better understand the potential SUA-lowering effects of amlodipine and perindopril, future research should use larger sample sizes and more accurate measurements, particularly in populations with specific comorbidities or concurrent medications that could affect uric acid metabolism.

Community pharmacies offering point-of-care testing represent an efficient method for the early identification and management of hyperuricemia, a condition increasingly associated with serious cardiovascular and kidney-related health issues and our study shows that such a service is feasible in Romania. By integrating POCT into these services, pharmacists can conduct rapid, on-site testing for non-communicable diseases (e.g. diabetes, hyper-tension, and etc) as well as communicable diseases (e.g. COVID-19, influenza etc). This approach facilitates early diagnosis, prompt treatment, and effective referral when necessary(85) .An economic study suggested that even a slight 3.5% increase in patient compliance with uric acid monitoring can render these services cost-effective (86). Thus, incorporating uric acid POCT into standard pharmacy services allows pharmacists to address diagnostic gaps, particularly in underserved areas, while fulfilling their expanding role in chronic disease screening and prevention.

Limitations

The main drawbacks of this study are its cross-sectional design and reliance on convenience sampling from a single geographic region (Călărași County), which limit the ability to confirm causal relationships and may affect the generalizability of the results to the wider Romanian population. The relatively low explained variance in the multivariable

regression model (R2 = 0.085) indicates that important unmeasured variables (such as specific dietary patterns, genetic factors (e.g., SLC2A9 or ABCG2 variants), and comprehensive indicators of kidney function, such as eGFR) were not included in this analysis.

The study also encountered difficulties due to missing data, especially regarding SUA measure-ments, mainly because the measurement kits were temporarily unavailable. Although multiple imputation by chained equations (MICE) was used to address this issue and preserve the distributional characteristics of the variables, a significant fraction of missing information (FMI = 0.44) persists, suggesting that some parameter uncertainty stems from the imputation process itself.

Moreover, the relatively small sample sizes in certain pharmacological subgroups, such as those receiving urate-lowering treatments or specific antihypertensives like amlodipine and perindopril, restricted the statistical power to identify minor yet potentially clinically important effects. Additionally, the inconsistent distribution of indapamide doses precluded a formal dose-response analysis, leaving the influence of specific diuretic concentrations on SUA levels unanswered in this cohort.

Conclusions

A significant occurrence of hyperuricemia (40.4%) was found among individuals visiting pharmacies in Southern Romania, in many cases among those without a previous diagnosis or those taking strong diuretics such as indapamide. Our findings indicate that although height is an independent biological factor associated with elevated serum uric acid levels, the use of loop and thiazide-like diuretics remains a key modifiable factor. The large number of undiagnosed cases underscores the essential role of community pharmacists in detecting individuals at risk through point-of-care testing. By incorporating screening services into standard pharmacy operations, healthcare professionals can promote earlier medical referrals and lifestyle changes, potentially decreasing the long-term impact of related cardiovascular, renal, and metabolic conditions.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Ethics approval and consent to participate

All experimental procedures were approved by the Ethics Committee of "Carol Davila" University of Medicine and Pharmacy (Approval Number 7462/14.03.2023). Informed consent was obtained from all patients included in the study.

AI use disclosure

Not applicable.

Conflict of interest

Velescu BS is a Managing Editor of the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

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